Delaware Medical Journal

Official Publication of the Medical Society of Delaware

ESTABLISHED 1776 — INCORPORATED 1789

DELAWARE HOSPITAL ISSUE...

Kanamycin, Stapes Mobilization,
Rhinoplasty, Coxsackie Group B
Infections in Children

VOLUME 32
NUMBER 2

FEBRUARY, 1960

Time after time...

in study after study

Once again, controlled sensitivity studies have demonstrated the efficacy of CHLOROMYCETIN. In one long-term study,[1] designed to eliminate variable factors in patterns of bacterial resistance, 5,600 consecutive cultures of gram-positive organisms were tested over a 16-month period. Of the four broad-spectrum antibiotics evaluated, CHLOROMYCETIN was consistently superior.

Reports from the literature[2-8] have repeatedly confirmed the observation that CHLOROMYCETIN is effective against a wide variety of clinically important pathogens. The marked susceptibility of gram-negative as well as gram-positive organisms to CHLOROMYCETIN suggests this antibiotic as an agent of choice in many infections.[3]

CHLOROMYCETIN (chloramphenicol, Parke-Davis) is available in various forms, including Kapseals® of 250 mg., in bottles of 16 and 100.

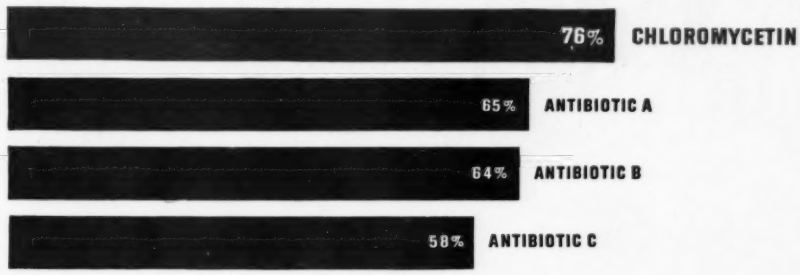
CHLOROMYCETIN is a potent therapeutic agent and, because certain blood dyscrasias have been associated with its administration, it should not be used indiscriminately or for minor infections. Furthermore, as with certain other drugs, adequate blood studies should be made when the patient requires prolonged or intermittent therapy.

CHLOROMYCETIN®

(chloramphenicol, Parke-Davis)

PROVES OUTSTANDINGLY EFFECTIVE AGAINST PROBLEM PATHOGENS

IN VITRO SENSITIVITY OF GRAM-POSITIVE COCCI FROM 5,600 CONSECUTIVE CULTURES TO CHLOROMYCETIN AND TO THREE OTHER BROAD-SPECTRUM ANTIBIOTICS*



REFERENCES: (1) Leming, B. H., Jr., & Flanigan, C., Jr., in Welch, H., & Marti-Ibãnez, F.: Antibiotics Annual 1958-1959, New York, Medical Encyclopedia, Inc., 1959, p. 414. (2) Goslings, W. R. O., & Buchli, K.: *Arch. Int. Med.* **102**:691, 1958. (3) Suter, L. S., & Ulrich, E. W.: *Antibiotics & Chemother.* **9**:38, 1959. (4) Metzger, W. I., in Welch, H., & Marti-Ibãnez, F.: Antibiotics Annual 1958-1959, New York, Medical Encyclopedia, Inc., 1959, p. 966. (5) Fischer, H. G.: *Deutsche med. Wchnschr.* **84**:257, 1959. (6) Borchardt, K. A.: *Antibiotics & Chemother.* **8**:564, 1958. (7) Schneierson, S. S.: *J. Mt. Sinai Hosp. New York* **25**:52, 1958. (8) Waisbren, B. A.: *Wisconsin M. J.* **57**:89, 1958.

*Adapted from Leming & Flanigan.[1]

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Delaware Medical Journal

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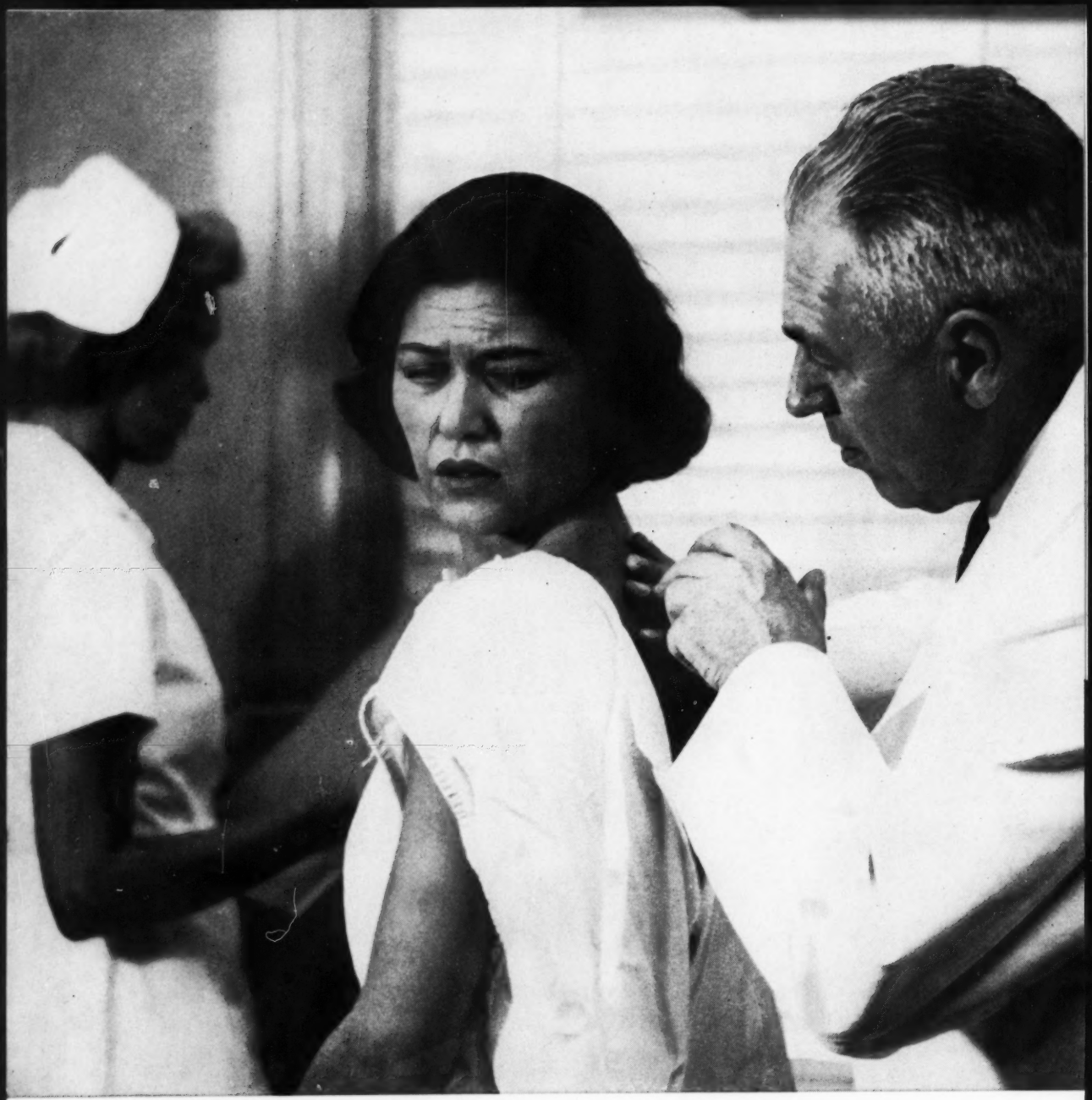


"I feel tired even after a full night's sleep."

Restores normal vitality in

emotional fatigue

Deprol relieves undue tiredness, apathy and depressed moods as it calms anxiety – without the risk of liver damage or extrapyramidal symptoms frequently reported with energizers or phenothiazines.

Emotional or nervous fatigue—undue tiredness, apathy, lethargy and listlessness—cuts sharply into the patient's usual physical and mental productivity. It is one of the most common conditions seen in every medical practice. Untreated, emotional fatigue may mushroom into a depressive episode, anxiety state, chronic fatigue or a mixture of these disorders.

Deprol acts fast to relieve emotional fatigue. It overcomes tiredness and lethargy, apathy and listlessness, thus restoring normal vitality and interest before the fatigue deepens. On Deprol, improvement is achieved without producing liver toxicity, hypotension, psychotic reactions, changes in sexual function or Parkinson-like reactions associated with energizers or phenothiazines.

BIBLIOGRAPHY (10 clinical studies, 714 patients):

1. Alexander, L. (35 patients): Chemotherapy of depression—Use of meprobamate combined with benactyzine(2-diethylaminoethyl benzilate) hydrochloride. J.A.M.A.**166**:1019, March 1, 1958. **2.** Bateman, J. C. and Carlton, H. N. (50 patients): Deprol as adjunctive therapy for patients with advanced cancer. Antibiotic Med. & Clin. Therapy. In press, 1959. **3.** Bell, J. L., Tauber, H., Santy, A. and Pulito, F. (77 patients): Treatment of depressive states in office practice. Dis. Nerv. System **20**:263, June 1959. **4.** Breitner, C. (31 patients): On mental depressions. Dis. Nerv. System **20**:142, (Section Two), May 1959. **5.** McClure, C. W., Papas, P. N., Speare, G. S., Palmer, E., Slattery, J. J., Konefal, S. H., Henken, B. S., Wood, C. A. and Ceresia, G. B. (128 patients): Treatment of depression—New technics and therapy. Am. Pract. & Digest Treat. **10**:1525, Sept. 1959. **6.** Pennington, V. M. (135 patients): Meprobamate-benactyzine (Deprol) in the treatment of chronic brain syndrome, schizophrenia and senility. J. Am. Geriatrics Soc. **7**:656, Aug. 1959. **7.** Rickels, K. and Ewing, J. H. (35 patients): Deprol in depressive conditions. Dis. Nerv. System **20**:364, (Section One), Aug. 1959. **8.** Ruchwarger, A. (87 patients): Use of Deprol (meprobamate combined with benactyzine hydrochloride) in the office treatment of depression. M. Ann. District of Columbia **28**:438, Aug. 1959. **9.** Settel, E. (52 patients): Treatment of depression in the elderly with a meprobamate-benactyzine hydrochloride combination. Antibiotic Med. & Clin. Therapy. In press, 1959. **10.** Splitter, S. R. (84 patients): The care of the anxious and the depressed. Submitted for publication, 1959.

and

11. Laughlin, H. P.: The Neuroses in Clinical Practice, Saunders, Philadelphia, 1956, pp. 448-481.

▲Deprol▲®

Dosage: Usual starting dose is 1 tablet q.i.d. When necessary, this may be gradually increased up to 3 tablets q.i.d.
Composition: 1 mg. 2-diethylaminoethyl benzilate hydrochloride (benactyzine HCl) and 400 mg. meprobamate.
Supplied: Bottles of 50 light-pink, scored tablets.

CD-482

WALLACE LABORATORIES · *New Brunswick, N. J.*

Tetracycline Phosphate Complex (TETREX®)
U.S. PAT. NO. 2,791,609
in the Therapy of PNEUMONIA

Preferably, antibiotic therapy should be based on pretreatment culture of the offending pathogen, but in bacterial pneumonia the problem may well be too pressing to permit the required delay of 24 to 48 hours. A differential diagnosis among bacterial pneumonias, based on such clinical grounds as speed of onset, sepsis and pain may guide the choice of antibiotic for initiation of therapy.

Should clinical judgment dictate that antibiotic therapy be started immediately, at the same time a sputum sample or a subglottic swab can be sent to the laboratory for culture and sensitivity studies. If the response to the first antimicrobial agent proves unsatisfactory, a reasonable basis for changing therapy will then be at hand.

Choosing the Antibiotic

Since therapy must be started at once for bacterial pneumonia, it is advisable to choose a broad-spectrum antibiotic that quickly produces high levels of active agent (e.g., tetracycline phosphate complex, TETREX). Such an antibiotic probably has the best chance of controlling the pathogen, whether it be gram-negative or gram-positive. And if the laboratory report shows that the invading organism is much less sensitive to tetracycline than to other agents, the patient can then be changed to an appropriate antibiotic. If the difference in sensitivity is slight, then the possibility of side effects, sensitization, and toxicity should be evaluated before changing therapy to another antibiotic.

The greatest number of bacterial pneumonias are caused by pneumococci, which respond very well to penicillin, tetracycline, and chloramphenicol. Also, these antibiotics are usually effective against the other gram-positive coccal pneumonias. But penicillin is ineffective against the viral pneumonias and the gram-negative *Hemophilus influenzae* and *Klebsiella pneumoniae*. Although *K. pneumoniae* causes only about 1 to 2 per cent of pneumonia cases on the average,[1] these are apt to be acute and fulminating (Friedländer's pneumonia), with a high mortality rate if not effectively treated. Since pneumococcal pneumonia may be difficult to distinguish clinically from Friedländer's, except by gram-stained sputum smear, it may be wiser to start treatment with an agent also effective against Klebsiella.

Penicillin, however, in addition to having a limited spectrum, also causes many minor and some serious sensitivity reactions. In a recent survey[2] it was found that penicillin produced severe skin reaction. But most important was the observation that anaphylactic shock, with a fatality rate of about 9 per cent, was the most frequent serious reaction. Such severe reactions are almost always associated with parenteral administration.

Tetracycline is also clinically effective in primary atypical pneumonia.[3]

The tetracyclines (e.g., TETREX) have the advantage of a broad range of antimicrobial activity and low toxicity. And in addition, the physician does not have to trouble himself or his patients with repeated blood studies when he prescribes TETREX. Minor reactions such as gastric upsets or mild skin rashes occur occasionally. The most serious side effects are staphylococcal and monilial overgrowth, but these are rare and can be adequately controlled.

No one would deny that appropriate antibiotic therapy has greatly reduced morbidity and saved many lives of patients with bacterial pneumonia. Nevertheless, general supportive measures in the care of patients remain important even today. Especially in the desperately ill patient, antibiotics are not considered as substitutes for the individual evaluation, clinical observation and judgment of the physician.

Some Micro-organisms Susceptible[a] to Tetracycline (TETREX)[b]

Streptococcus; Staphylococcus; Pneumococcus; Gonococcus; Meningococcus; *C. diphtheriae; B. anthracis; E. coli;* Proteus; *A. aerogenes; Ps. aeruginosa; K. pneumoniae;* Shigella; Brucella; *P. tularensis; H. influenzae; T. pallidum;* Rickettsiae; Viruses of psittacosis and ornithosis, lymphogranuloma inguinale, primary atypical pneumonia; *E. histolytica; D. granulomatosis.*

a Some strains are not susceptible.

b Table adapted from Goodman, L. S., and Gilman, A.: The Pharmaceutical Basis of Therapeutics. 2nd edition, New York, The Macmillan Co., 1956, pp. 1322-1323.

References: 1. Wood, W. E., Jr.: In: A Textbook of Medicine. Edited by Cecil, R. L., and Loeb, R. F., 9th edition, Philadelphia, W. B. Saunders Co., 1955, p. 145. 2. Welch, H.; Lewis, C. H.; Weinstein, H. I., and Boeckman, B. B.: Severe reactions to antibiotics. A nationwide survey. Antibiotic Med. & Clin. Ther. **4**:800 (Dec.) 1957. 3. Keefer, C. S.: The choice of an anti-infective agent. In: Drugs of Choice, 1958-1959. Edited by Walter Modell, St. Louis, The C. V. Mosby Co., 1958, p. 135.

it started as a "cold"...

to prevent the sequelae of u.r.i. ... and relieve the symptom complex

ACHROCIDIN®

Tetracycline-Antihistamine-Analgesic Compound Lederle

Pneumonitis, otitis, tonsillitis, adenitis, sinusitis or bronchitis develops as a serious bacterial complication in about one in eight cases of acute upper respiratory infection.[1] To protect and relieve the "cold" patient... ACHROCIDIN.

Usual dosage: 2 tablets or teaspoonfuls q.i.d. (equiv. 1 Gm. tetracycline). Each TABLET contains: ACHROMYCIN® Tetracycline (125 mg.); phenacetin (120 mg.); caffeine (30 mg.); salicylamide (150 mg.); chlorothen citrate (25 mg.). Also as SYRUP (lemon-lime flavored), caffeine-free.

1. Based on estimate by Van Volkenburgh, V. A., and Frost, W. H.: Am. J. Hygiene 71:122 (Jan.) 1933

Lederle LEDERLE LABORATORIES, a Division of AMERICAN CYANAMID COMPANY, Pearl River, New York

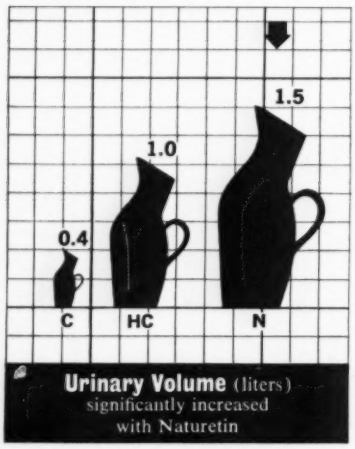
more closely approaches the ideal diuretic

Naturētin

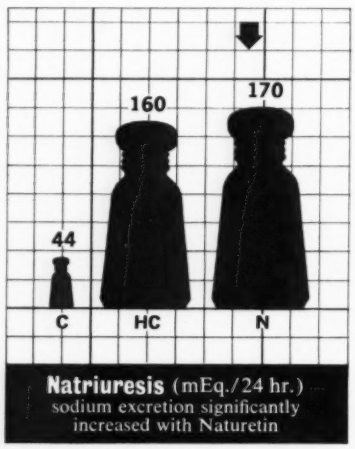
Squibb Benzydroflumethiazide

"When compared to other members of this heterocyclic group of compounds, this drug [NATURETIN] shows a significantly increased natriuresis and decreased loss of potassium and bicarbonate. In this respect it more closely approaches a natural or 'ideal diuretic.' It is effective upon continuous administration and causes no significant serum biochemical changes. It is effective in a wide variety of edematous and hypertensive states and represents a significant advance in diuretic therapy." *Ford, R.V.: Pharmacological observations on a more potent benzothiadiazine diuretic; accepted for publication by the American Heart Journal.*

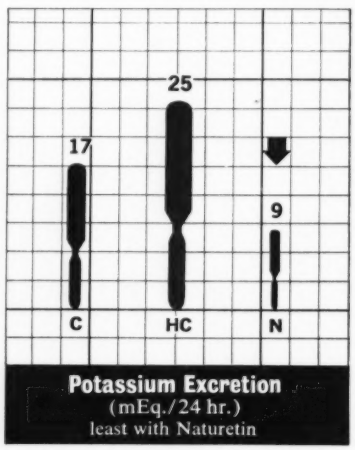
Comparison of electrolyte excretion pattern for the 24 hours following typical doses of chlorothiazide, hydrochlorothiazide, and Naturetin[1]



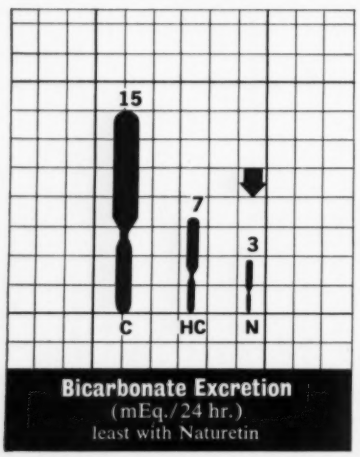
Urinary Volume (liters) significantly increased with Naturetin



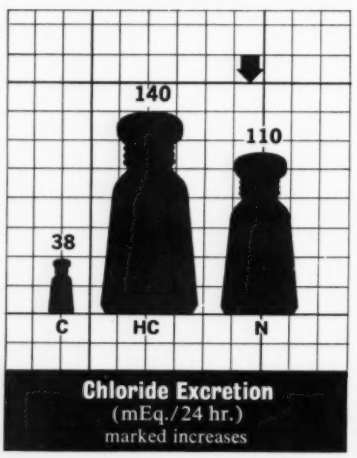
Natriuresis (mEq./24 hr.) sodium excretion significantly increased with Naturetin



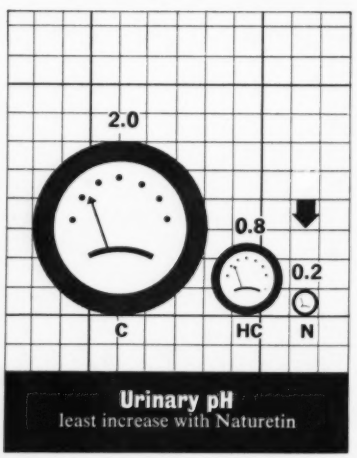
Potassium Excretion (mEq./24 hr.) least with Naturetin



Bicarbonate Excretion (mEq./24 hr.) least with Naturetin



Chloride Excretion (mEq./24 hr.) marked increases



Urinary pH least increase with Naturetin

Typical Doses: Chlorothiazide—1,000 mg.; Hydrochlorothiazide—50 mg.; Naturetin (Benzydroflumethiazide)—5 mg.

Adapted from: Ford, R. V., Squibb Clin. Res. Notes 2:1 (Dec.) 1959.

A single 5 mg. tablet once a day provides all these advantages[2]

- prolonged action – in excess of 18 hours
- convenient once-a-day dosage
- low daily dosage – more economical for the patient
- no significant alteration in normal electrolyte excretion pattern
- repetitively effective as a diuretic and antihypertensive
- greater potency mg. for mg.—more than 100 times as potent as chlorothiazide
- potency maintained with continued administration
- low toxicity – few side effects – low salt diets not necessary
- comparative studies with chlorothiazide, hydrochlorothiazide, and Naturetin disclose that smallest doses of Naturetin produce greater weight loss per day
- in hypertension, Naturetin, alone or in combination with other antihypertensives, produces significant decreases in mean blood pressure and other favorable clinical effects
- purpura and agranulocytosis not observed
- allergic reactions rarely observed

[2]Reports (1959) to the Squibb Institute for Medical Research.

Naturētin – *Indications:* in control of edema when diuresis is required, in congestive heart failure, in the premenstrual syndrome, nephrosis and nephritis, cirrhosis with ascites, edema induced by drugs (certain steroids); in the management of hypertension, used alone, combined with Raudixin (Squibb Rauwolfia Serpentina Whole Root), or with other antihypertensive drugs, such as ganglionic blocking agents.

Contraindications: none, except in complete renal shutdown.

Precautions: when Naturetin is added to an antihypertensive regimen including hydralazine, veratrum, and/or ganglionic blocking agents, immediate reduction must be made in the dosage for all preparations; the dosage for ganglionic blocking agents must be decreased by 50% to avoid a precipitous drop in blood pressure. This also applies if these hypotensive drugs are added to an established Naturetin regimen . . . in hypochloremic alkalosis with or without hypokalemia . . in cirrhotic patients or those on digitalis therapy when reductions in serum potassium are noted . . in diabetic patients or those predisposed to diabetes . . . when increased uric acid concentrations are noted . . . when signs—leg or abdominal cramps, pruritus, paresthesia, rash—suggestive of hypersensitivity, are noted.

Naturētin – *Dosage: in edema,* average dose, 5 mg., once daily, preferably in the morning; to initiate therapy, up to 20 mg., once daily or in divided doses; for maintenance, 2.5 to 5.0 mg., daily in a single dose. *In hypertension:* suggested initial dose, 5 to 20 mg. daily; for maintenance, 2.5 to 15 mg. daily, depending on the individual response of the patient. When Naturetin is added to an antihypertensive regimen with other agents, lower maintenance doses of each drug should be used.

Naturētin – *Supplied:* tablets of 2.5 mg. and 5 mg. (scored).

SQUIBB

Squibb Quality—the Priceless Ingredient

Rx Naturetin 5mg. Disp. #30 Sig: 1 each morning

'RAUDIXIN'® AND 'NATURETIN' ARE SQUIBB TRADEMARKS.

Q

Shouldn't **KANTREX**® Injection* be kept in reserve for treating staph or gram-negative infections until other antibiotics have been tried first?

a

No. Naturally, KANTREX Injection should not be used in mild or self-limited infections, but as Yow states, "it should not be withheld in moderately severe or severe infections."[1]

Q *What properties of* KANTREX *led Yow to draw this conclusion?*

Next page, please . . .

*Kanamycin sulfate injection (Bristol)

MORE QUESTIONS on the clinical use of KANTREX®

Q *What properties of* KANTREX *led Yow to draw this conclusion?*

a The following[2]: (1) KANTREX Injection is bactericidal, not merely bacteriostatic; (2) it is absorbed rapidly after intramuscular injection; (3) it has proved successful in many types of staph and gram-negative infections resistant to other antibiotics; and (4) it is well tolerated when used judiciously.

Q *But if I use* KANTREX *Injection, won't that help make bacteria resistant to it?*

a Numerous investigators have reported that micro-organisms do not readily develop resistance to KANTREX in a clinical setting; and emergence of resistance to KANTREX has not been a practical problem.[3,4,5,6,7,8]

Q *How does the* in vitro *activity of* KANTREX *against staph compare with that of other antibiotics?*

a Griffith and Ostrander[9] tested 794 strains of staphylococci and found that 95.2% were sensitive to KANTREX. By contrast, only 15.5% of the same organisms were sensitive to penicillin, 33.5% to tetracycline, 52.4% to erythromycin, and 71.7% to chloramphenicol.

Q *What about the sensitivity of other pathogens to* KANTREX*?*

a Leming[10] recently summarized the *in vitro* activity of KANTREX against 4493 strains of various organisms isolated from hospital patients over a 7-month period. He reported that the following percentages of these clinical isolates were sensitive to KANTREX: *Proteus mirabilis*, 98%; *Proteus morganii*, 94%; *Proteus rettgeri*, 89%; *Proteus vulgaris*, 87%; *Paracolobactrum intermedium*, 96%; *Coli-aerogenes* group, 93%; *Streptococcus viridans*, 78%; *Salmonella* and *Shigella*, 92%.

Q *What do these figures mean clinically?*

a A great deal. As Yow stated in recent reviews of KANTREX Injection, it "appears to be one of the

most effective anti-staphylococcal antibiotics available today."[1,2] KANTREX Injection is also effective in the treatment of infections caused by "most strains of *E. coli, Proteus sp.*, the *Klebsiella pneumoniae-Aerobacter aerogenes* group, and many strains of *Pseudomonas aeruginosa* resistant to other antibiotics."[2] In another report, KANTREX Injection was placed at the head of the list of drugs "with the most chance of success" against *A. aerogenes* urinary tract infections.[11]

Q *Have these findings about* KANTREX *therapy been substantiated by other investigators?*

a Yes, indeed. Finegold,[12] who reviewed the clinical findings of 64 investigators, reported that infections which "usually responded" to KANTREX included: staph infections (including staph enteritis), *E. coli* infections (including *E. coli* gastroenteritis), atypical acid-fast bacillus infections, *Aerobacter-Klebsiella* infections, paracolon infections, *Alcaligenes* infections, *Shigella* dysentery, *Salmonella* enteritis, anthrax, amebiasis, and *E. histolytica* carrier state. Among the infections that "sometimes responded" were listed: pneumococcal infections, group A *beta*-hemolytic streptococcic infections, *Proteus* infections, gonorrhea, and paratyphoid fever.

Q *That's an impressive list. What didn't respond?*

a According to Finegold's tabulation, treatment failures were "usually" encountered in brucellosis, *Pseudomonas* infections, typhoid fever, mycotic infections and anaerobic infections.[12]

Q *How long do I have to give* KANTREX *Injection before I know whether it works or not?*

a Generally 2 or 3 days or less. Usually the effectiveness of KANTREX Injection can be determined in 24 to 36 hours. Rutenburg et al. reported that "the rapidity with which bacteria are killed by this agent is reflected by the promptness of the clinical response."[13]

Q *How long should I continue to administer* KANTREX?

a If definite clinical response does not occur within 5 days, KANTREX therapy should be stopped and the antibiotic sensitivity of the invading organism rechecked.

Q *What is the hazard of a patient developing hearing loss during* KANTREX *therapy?*

a In well hydrated patients with normal kidney function receiving KANTREX at the recommended dosage schedule, the hazard of ototoxic reactions is negligible. In patients with impaired kidney function, the risk of ototoxic reactions is sharply increased, and in such cases the dosage should be reduced. Finegold has stated: "Toxicity inherent in the drug can be avoided or minimized with careful management."[12]

Q *Why should renal impairment influence the dosage?*

a Because renal impairment delays the excretion of KANTREX Injection and causes an excessive accumulation in blood and tissues. Such excessive concentrations increase the risk of ototoxicity. Dosage recommendations emphasize that adequate serum levels can be achieved in such patients with a fraction of the dose suggested for patients with normal kidney function.

Q *Have you had any reports of blood dyscrasias?*

a None whatever.

Q *You mean, then, that a physician who uses* KANTREX *Injection judiciously should find it not only effective but also well tolerated?*

a Effective? Certainly, against almost all staph or "gram-negatives," even though they may be resistant to other antibiotics. Well tolerated? Yes, when given in recommended dosage. The physician can well agree with Yow, that while KANTREX Injection should not be used in mild or self-limited infections, "it should not be withheld in moderately severe or severe infections."[1] That, indeed, is the time to give it—first!

KANTREX® CAPSULES

for local gastrointestinal therapy...
not for systemic infections

Q *If* KANTREX *is not absorbed from the G.I. tract, what are the capsules used for?*

a Preoperative bowel sterilization, and local treatment of intestinal infections due to kanamycin-sensitive organisms.

Q *What types of intestinal infections, for instance?*

a Acute and chronic shigellosis,[14] acute and chronic salmonellosis,[4,14,15,16] amebiasis,[17] bacillary dysentery,[18] infantile diarrhea,[16,18] gastroenteritis,[19] and staphylococcal enterocolitis.[2]

Q *For preoperative bowel sterilization, why should I switch from neomycin to* KANTREX *Capsules?*

a Because KANTREX has been rated superior to neomycin for this purpose.[20,21,22] Out of 30 intestinal antiseptics studied, KANTREX was designated "the only single agent classified as a preferred drug."[21] KANTREX "consistently eliminated all aerobic bacteria within 72 hours (and often within 24 to 36 hours) if a purgative was given with the first dose to expedite passage through the gastrointestinal tract."[12]

Q *Is that all the advantage* KANTREX *has over neomycin for preoperative bowel sterilization?*

a Not at all, there are several others. Diarrhea, nausea and vomiting have not been observed with KANTREX, though they occur frequently with neomycin; yeasts do not proliferate, in contrast to rapid growth with neomycin; and clostridia are well controlled with KANTREX, and not controlled with neomycin.[20,21,22]

KANTREX®

INJECTION KANAMYCIN SULFATE INJECTION

INDICATIONS

Infections due to kanamycin-sensitive organisms, particularly staph or "gram-negatives": genito-urinary infections; skin, soft tissue and post-surgical infections; respiratory tract infections; septicemia and bacteremia; osteomyelitis and periostitis; staph enteritis and gastroenteritis.

DOSAGE: INTRAMUSCULAR ROUTE

Usual daily dose is 15 mg. per kg. of body weight, in 2 to 4 divided doses. (See detailed recommendations in insert accompanying each package.)

TOXICITY

When dosage recommendations are followed, the incidence of toxic reactions to KANTREX is low. In well hydrated patients under 45 years of age with normal kidney function, receiving a total dose of 20 Gm. or less of KANTREX, the risk of severe ototoxic reactions is negligible.

In patients with impaired renal function or pre-renal azotemia, the daily dose of KANTREX should be reduced to avoid accumulation of the drug in serum and tissues, thus minimizing the possibility of ototoxicity. In such patients, if therapy is expected to last 5 days or more, audiograms should be obtained prior to and during treatment. KANTREX therapy should be stopped if tinnitus or subjective hearing loss develops, or if audiograms show significant loss of high frequency response.

OTHER ROUTES OF ADMINISTRATION

KANTREX should be used by intravenous infusion only when the intramuscular route is impracticable. KANTREX can also be employed for intraperitoneal use, aerosol treatment, and as an irrigating solution. See package insert for directions.

PRECAUTIONS

Use of antibiotics may occasionally result in overgrowth of non-sensitive organisms. If superinfection appears during therapy, appropriate measures should be taken.

SUPPLY

Available in rubber-capped vials as a ready-to-use sterile aqueous solution in two concentrations (stable at room temperature indefinitely):

KANTREX Injection, 0.5 Gm. kanamycin (as sulfate) in 2 ml. volume.
KANTREX Injection, 1.0 Gm. kanamycin (as sulfate) in 3 ml. volume.

CAPSULES (for local gastrointestinal therapy; not for systemic medication)

INDICATIONS AND DOSAGE

For preoperative bowel sterilization: 1.0 Gm. (2 capsules) every hour for 4 hours, followed by 1.0 Gm. (2 capsules) every 6 hours for 36 to 72 hours.

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PRECAUTION

Preoperative use of KANTREX Capsules is contraindicated in the presence of intestinal obstruction. Although only negligible amounts of KANTREX are absorbed through intact intestinal mucosa, the possibility of increased absorption from ulcerated or denuded areas should be considered.

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KANTREX Capsules, 0.5 Gm. kanamycin (as sulfate), bottles of 20 and 100.

REFERENCES:

1. Yow, E. M.: Antibiotic Therapy for Staphylococcal Diseases, H. Welch and M. Finland, eds., Medical Encyclopedia, New York, 1959, p. 167. 2. Yow, E. M.: Practitioner 182:759, 1959. 3. Davies, F. G.: Ann. N. Y. Acad. Sci. 76:129, 1958. 4. Finegold, S. M., et al.: *Ibid.* 76:319, 1958. 5. Finegold, S. M., et al.: Antibiotics Annual 1958-9, p. 606. 6. Greey, P. H., and Wightman, K. J. R.: Annals N. Y. Acad. Sci. 76:224, 1958. 7. Huang, A. A., Sarria, A., and High, R. H.: Antibiotics Annual 1958-9, p. 687. 8. Yow, E. M., and Monzon, O. T.: Annals N. Y. Acad. Sci. 76:372, 1958. 9. Griffith, L. J., and Ostrander, W. E.: Ant. & Chemo. 9:416, 1959. 10. Leming, B. H., Jr.: Personal communication. 11. Lattimer, J. K., et al.: J.A.M.A. 170:988, 1959. 12. Finegold, S. M.: A.M.A. Arch. Int. Med. 104:15, 1959. 13. Rutenburg, A. M., et al.: Ann. N. Y. Acad. Sci. 76:348, 1958. 14. Thurman, W. G., and Platou, R. V.: *Ibid.* 76:280, 1958. 15. Yow, E. M., and Monzon, O. T.: Antibiotics Annual 1958-9, p. 736. 16. Thurman, W. G., and Platou, R. V.: Antibiotics Annual 1958-9, p. 806. 17. Ruiz Sanchez, F., et al.: *Ibid.*, p. 725. 18. Fujii, R., et al.: World-wide Abst. Gen. Med. 2:28, 1959. 19. High, R. H., Sarria, A., and Huang, N. N.: Ann. N. Y. Acad. Sci. 76:289, 1958. 20. Cohn, I., Jr.: *Ibid.* 76:212, 1958. 21. Cohn, I., Jr., and Longacre, A. B.: Antibiotics Annual 1958-9, p. 761. 22. Cohn, I., Jr., and Longacre, A. B.: S. G. & O. 108:100, 1959.

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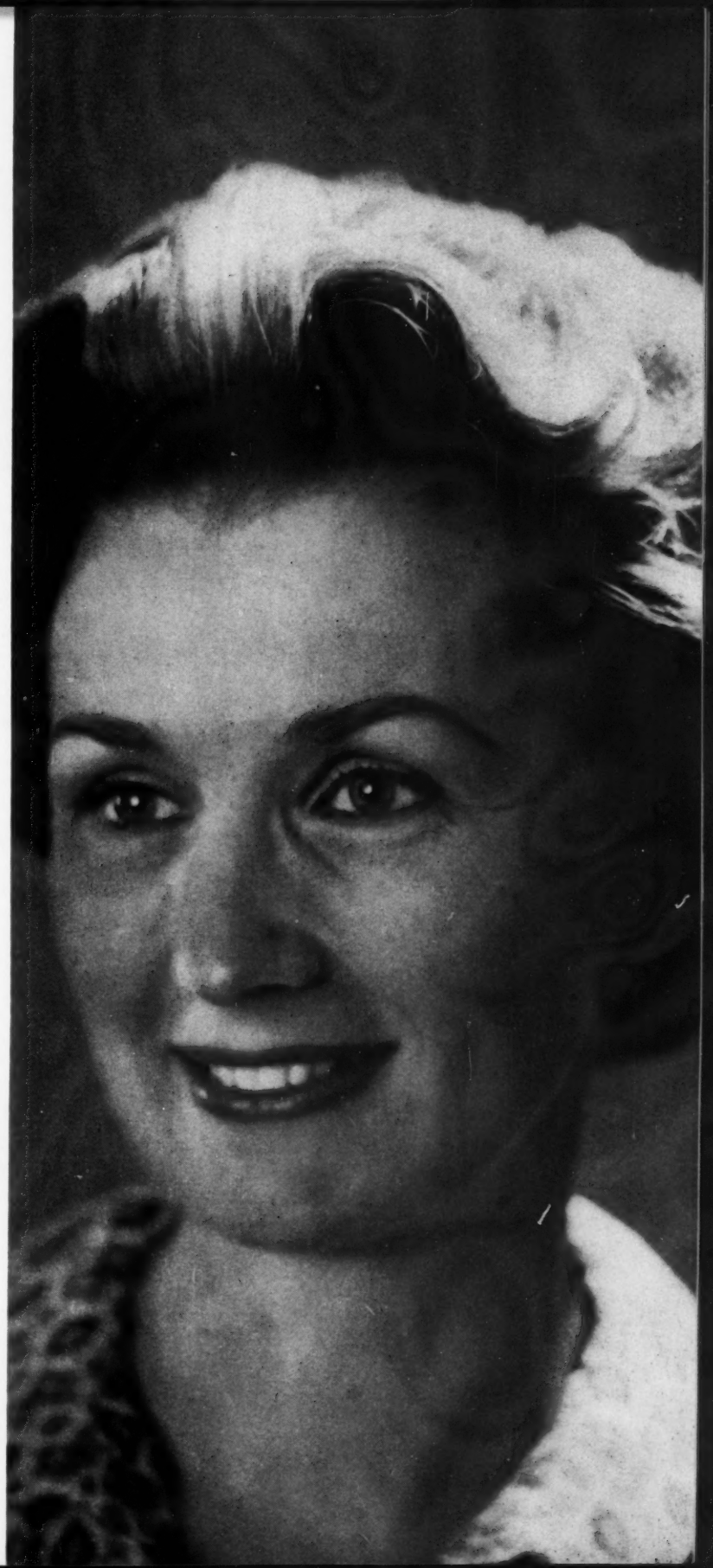

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REFERENCES:

1-11. Papers read at Seventh Symposium on Antibiotics, Washington, D. C., November 4-6, 1959.

12. Phillips, F. M.: DECLOMYCIN—Seventh Interim Report. Department of Clinical Investigation, Lederle Laboratories, Pearl River, N. Y., December 4, 1959.

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genitourinary infection. Roberts, M. S.; Seneca, H., and Lattimer, J. K.,[1] New York, N. Y.–Ninety-one per cent of the Gram-positive and 27 per cent of the Gram-negative, among 66 organisms cultured from genitourinary infection, responded to DECLOMYCIN. Serum antibiotic activity was found three times greater than with tetracycline.

toleration. Boger, W. P., and Gavin, J. J.,[2] Norristown, Pennsylvania–Side effects with DECLOMYCIN were minimal. When dosage was 0.5 to 1 Gm. daily in divided doses, only two of 82 patients exhibited nausea.

activity level sustentation. Kunin, C. M.; Dornbush, A. C., and Finland, M.,[3] Boston, Massachusetts–Of the four tetracycline analogues, DECLOMYCIN Demethylchlortetracycline showed the longest sustained activity levels in the blood.

gonococcal infection. Marmell, M., and Prigot, A.,[4] New York, N. Y.–Of 63 cases of gonorrhea, 61 promptly responded after short courses of DECLOMYCIN. Therapeutic effect was found equal to that of intramuscular penicillin.

bronchopulmonary infection. Perry, D. M.; Hall, G. A., and Kirby, W. M. M.,[5] Seattle, Washington–Of 30 cases of acute bacterial pneumonia, all were afebrile following two to 10 days of treatment with DECLOMYCIN. Results were good in 21.... All of six patients with acute bronchitis responded promptly.

pediatric infection. Fujii, R.; Ichihashi, H.; Minamitani, M.; Konno, M., and Ishibashi, T.,[6] Tokyo, Japan–In 309 pediatric patients with various infections, DECLOMYCIN was effective in 75 per cent.

urogenital infection. Vineyard, J. P.; Hogan, J., and Sanford, J. P.,[7] Dallas, Texas–Clinical response in pyelonephritis correlated well with results of *in vitro* sensitivity tests, which showed some strains of *A. aerogenes*, Proteus and Pseudomonas more susceptible to DECLOMYCIN Demethylchlortetracycline than to its analogues.

pneumonia. Duke, C. J.; Katz, S., and Donohoe, R. F.,[8] Washington, D. C.–Results were satisfactory in all but two of 32 cases of acute bacterial pneumonia, of which only 11 were uncomplicated. No side effects were observed.

brucellosis. Chávez Max G.,[9] Mexico, D. F., Mexico–All of nine patients with *Br. melitensis* infection were afebrile after five days on DECLOMYCIN. Blood cultures were negative in all cases on the 20th day. Side effects were limited to slight temperature increases which abated in four days.

pustular dermatosis. Blau, S., and Kanof, N. B.,[10] New York, N. Y.–Results with DECLOMYCIN were excellent in both of two cases of impetigo, one of two cases of folliculitis, six of nine cases of furunculosis, all of three cases of acne rosacea and 26 of 45 cases of acne vulgaris. Overall, results were excellent or good in 85 per cent.

antibacterial spectrum. Finland, M.; Hirsch, H. A., and Kunin, C. M.,[11] Boston, Massachusetts–DECLOMYCIN Demethylchlortetracycline was found the most effective of the tetracycline analogues against two-thirds of 680 normally sensitive strains of 15 separate species.

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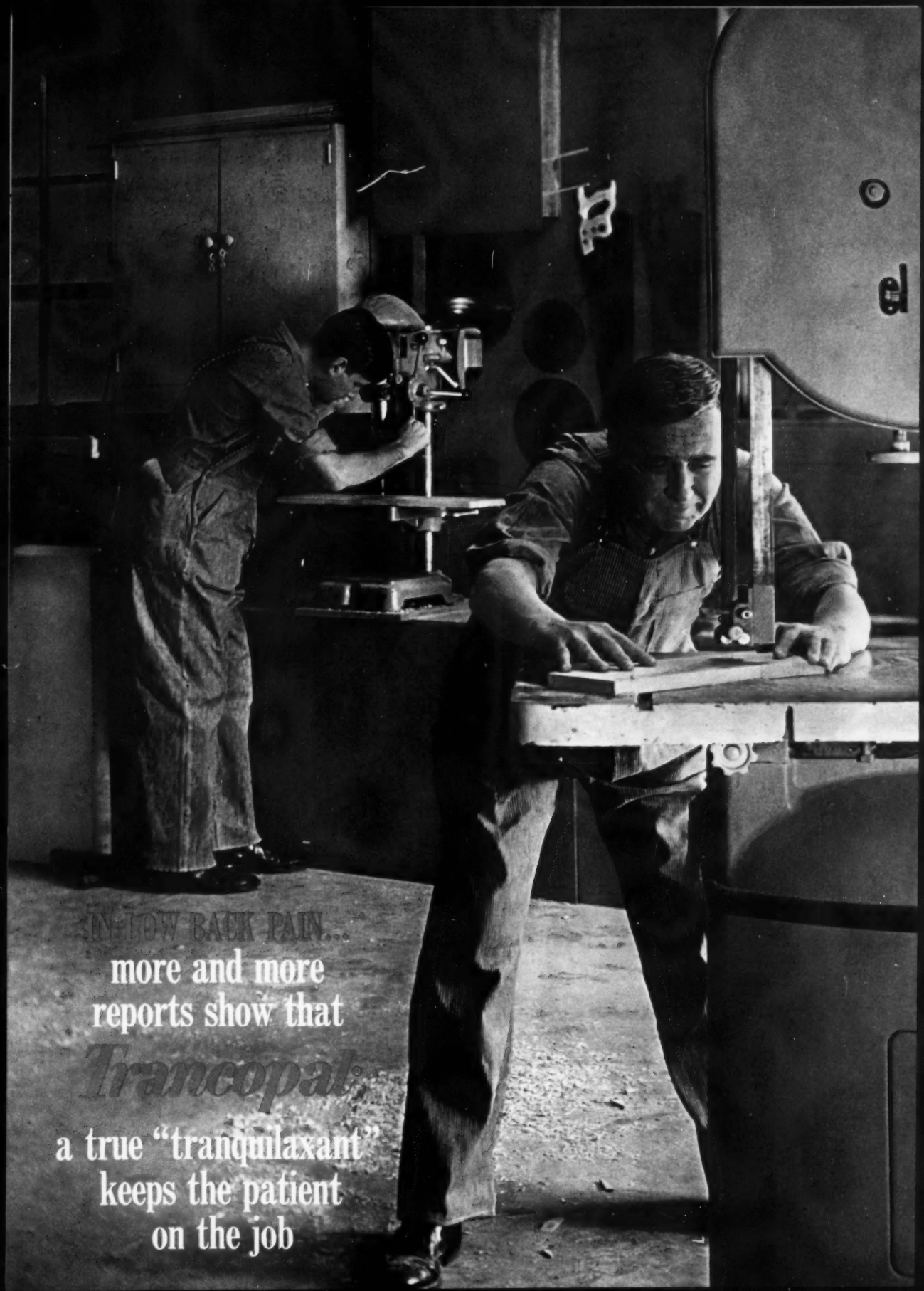
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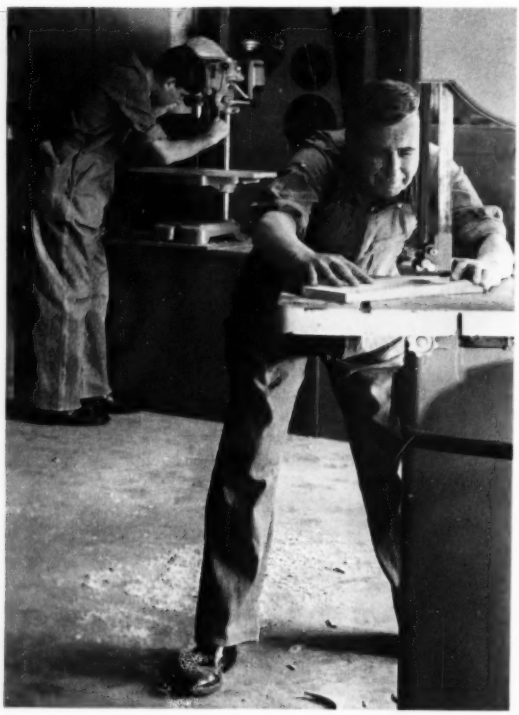

Impressive numbers of patients with low back pain and other musculospastic conditions treated with Trancopal have been freed of symptoms and enabled to return to their usual activities, according to newly published clinical reports. In a recent study by Lichtman,[1] Trancopal brought excellent to satisfactory muscle relaxation to 817 of 879 patients. The patients in this group suffered from skeletal muscle spasm associated with low back pain (361 cases), stiff neck (128 cases), bursitis (177 cases), and other skeletal muscle disorders (213 cases). Side effects were rare (2 per cent of patients), and it was not necessary to discontinue medication in any of the patients. Lichtman comments: "Chlormethazanone [Trancopal] not only relieved painful muscle spasm, but allowed the patients to resume their normal activities with no interference in performance of either manual or intellectual tasks."[2]

When you prescribe Trancopal for musculoskeletal disorders, you can confidently expect that your patients will be relieved of the pain and stiffness. You can be sure of their speedy return to everyday work and recreation.

Mullin and Epifano call Trancopal "...a very effective skeletal muscle spasmolytic."[3] They found that Trancopal brought good to excellent relief to all of 39 patients with skeletal muscle spasm related to trauma, bursitis, rheumatoid arthritis, osteoarthritis, and intervertebral disc syndrome. (No side effects were noted except that one patient had slight dryness of the mouth.)

The pattern is similar in every new series reported: Ganz,[4] DeNyse,[5] Shanaphy[6] and Stough.[7]

Trancopal is a true "tranquilaxant"

Trancopal "...combines the properties of tranquilization and skeletal muscle relaxation with no concomitant change in normal consciousness."[6]

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Alleviates tension

And, of course, Trancopal is also very useful in the treatment of patients in anxiety and tension states. As Ganz says, "...a most valuable drug for relieving tension, apprehension and various psychogenic states...allows the patient to use his energies in a more productive manner in overcoming his basic problems."[4]

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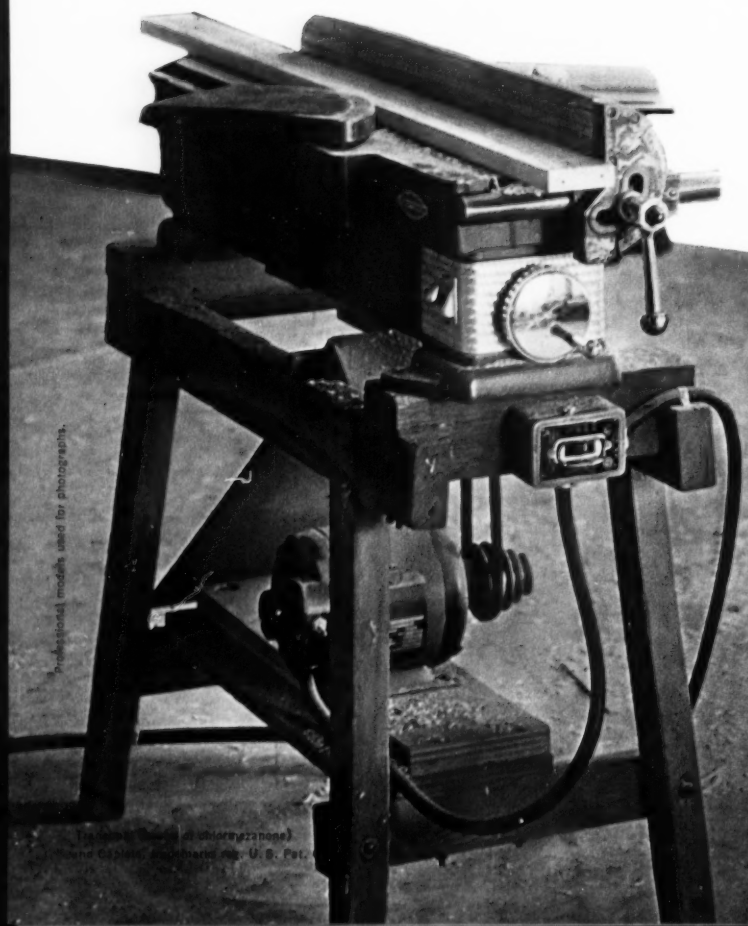

Professional models used for photographs.

References: 1. Lichtman, A. L.: Scientific Exhibit, meeting of the International College of Surgeons, Miami Beach, Fla., Jan. 4-7, 1959. 2. Lichtman, A. L.: *Kentucky Acad. Gen. Pract. J.* 4:28, Oct., 1958. 3. Mullin, W. G., and Epifano, Leonard: *Am. Pract. & Digest Treat.* 10:1743, Oct., 1959. 4. Ganz, S. E.: *J. Indiana M. A.* 52:1134, July, 1959. 5. DeNyse, D. L.: *M. Times* 87:1512, Nov., 1959. 6. Shanaphy, J. F.: *Current Therap. Res.* 1:59, Oct., 1959. 7. Stough, A. R.: *J. Oklahoma M. A.* 52:575, Sept., 1959.

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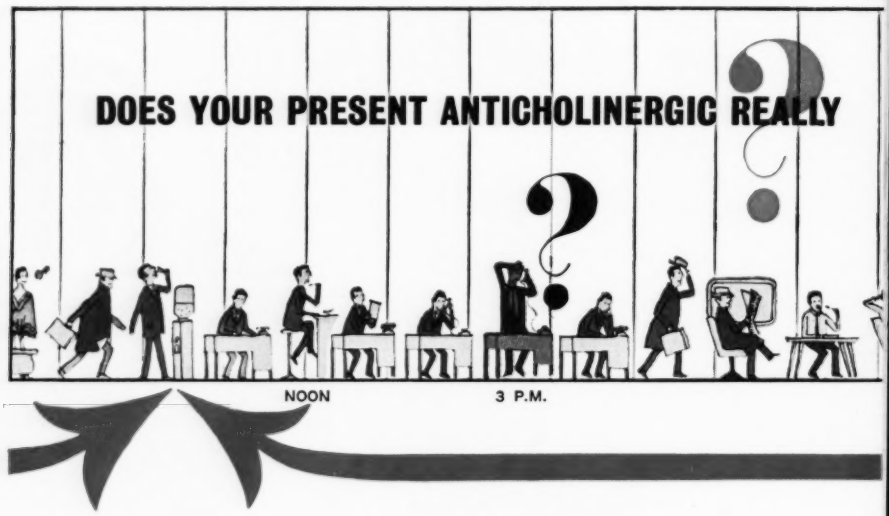

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McHardy: "[Oxyphencyclimine] has proved to be an excellent sustained-action anticholinergic in our study of this agent over a period of eighteen months."[1]

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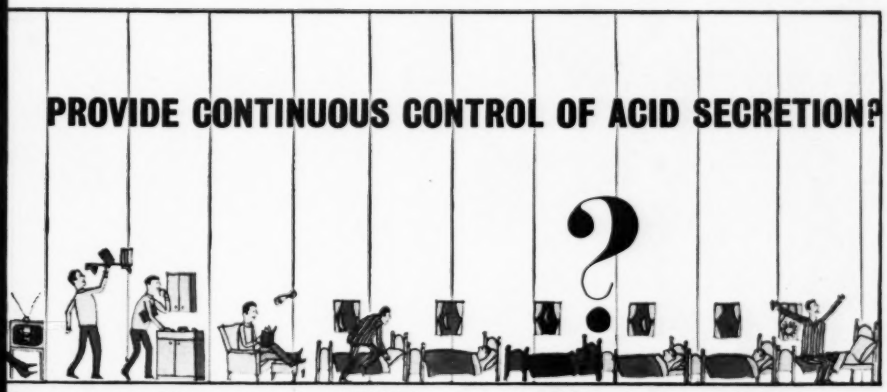

"Prolonged periods of achlorhydria" after 10 mg. oxyphencyclimine q. 12 h.[2]

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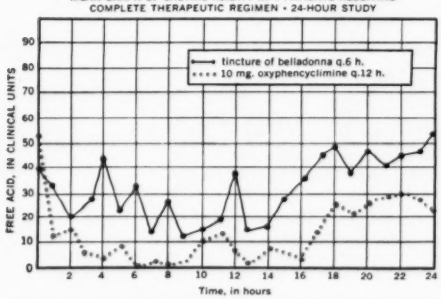

Clinical Diagnosis: Peptic Ulcer—Gastritis—Gastroenteritis—Colitis—Functional Bowel Syndrome—Duodenitis—Hiatus Hernia (symptomatic)—Irritable Bowel Syndrome—Pylorospasm—Cardiospasm—Biliary Tract Dysfunctions—and Dysmenorrhea.

Clinical Results: Effective in over 92% of cases.

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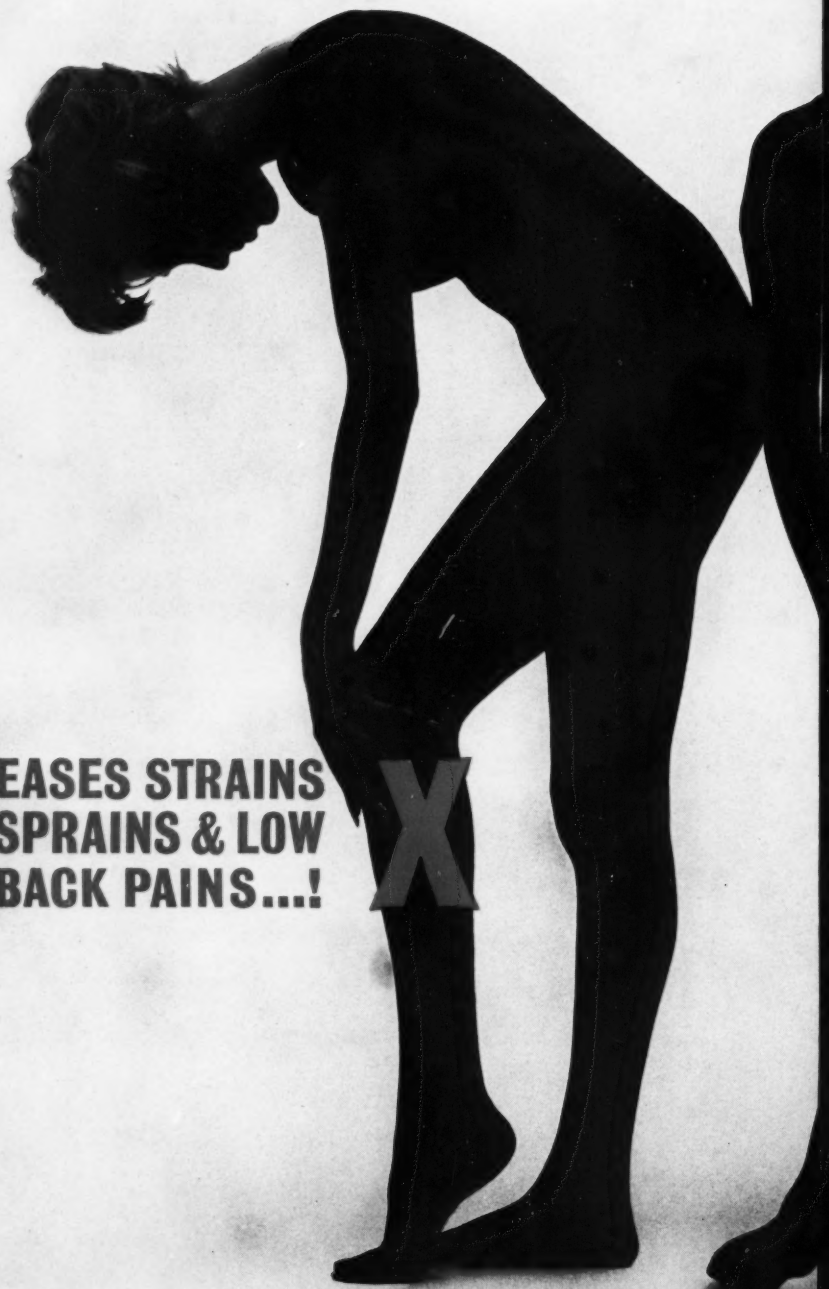

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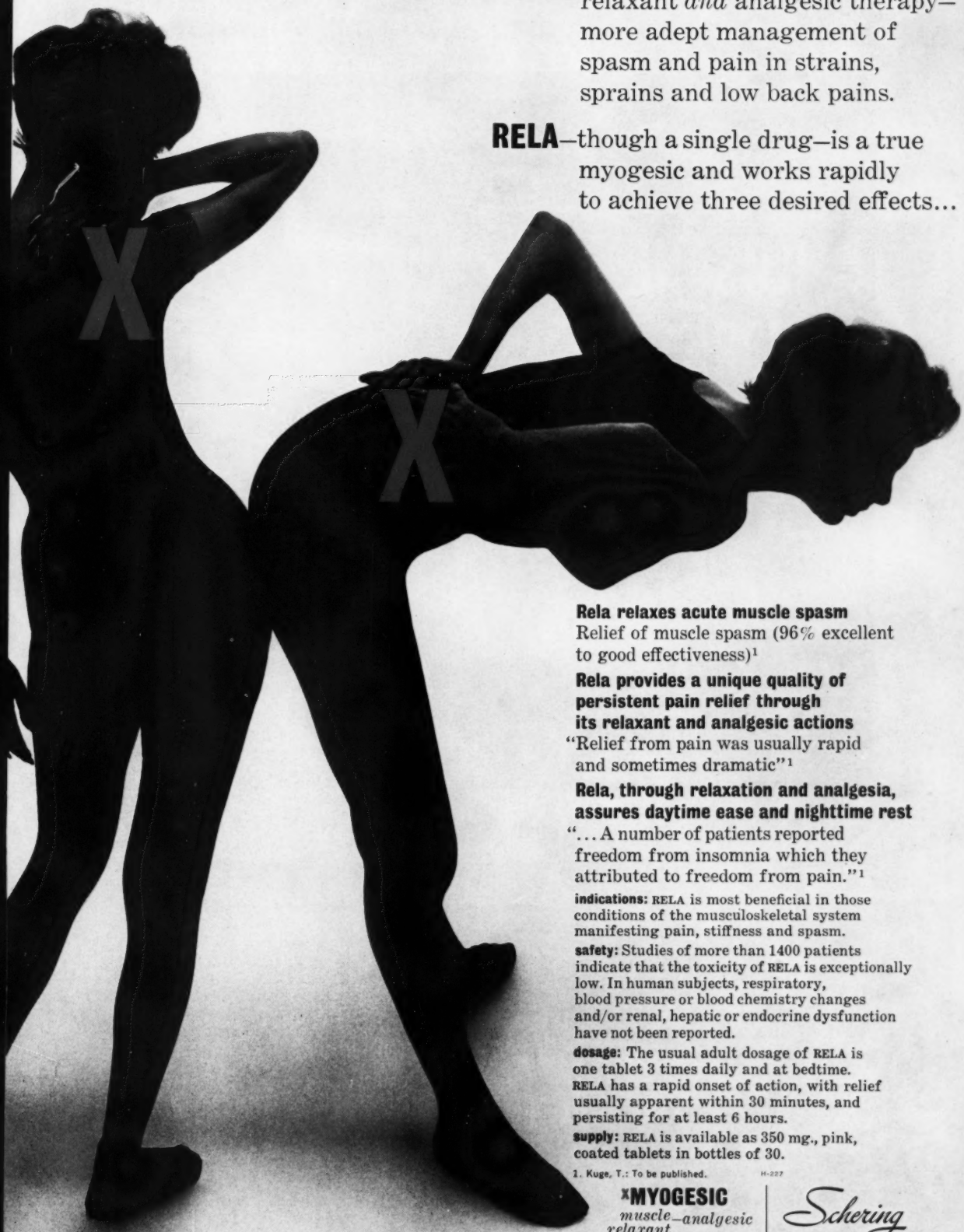

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Rela relaxes acute muscle spasm
Relief of muscle spasm (96% excellent to good effectiveness)[1]

Rela provides a unique quality of persistent pain relief through its relaxant and analgesic actions
"Relief from pain was usually rapid and sometimes dramatic"[1]

Rela, through relaxation and analgesia, assures daytime ease and nighttime rest
"... A number of patients reported freedom from insomnia which they attributed to freedom from pain."[1]

indications: RELA is most beneficial in those conditions of the musculoskeletal system manifesting pain, stiffness and spasm.

safety: Studies of more than 1400 patients indicate that the toxicity of RELA is exceptionally low. In human subjects, respiratory, blood pressure or blood chemistry changes and/or renal, hepatic or endocrine dysfunction have not been reported.

dosage: The usual adult dosage of RELA is one tablet 3 times daily and at bedtime. RELA has a rapid onset of action, with relief usually apparent within 30 minutes, and persisting for at least 6 hours.

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1. Kuge, T.: To be published.

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VOLUME 32 FEBRUARY, 1960 NUMBER 2

KANAMYCIN

A CLINICAL STUDY

● Kanamycin is an effective agent in the treatment of infections due to staphylococci and some gram-negative organisms. However, toxicity is frequent enough to limit widespread use of this drug.

W. J. Holloway, M.D.*
R. S. Kahlbaugh, M.D.**
E. G. Scott, M.T.***

Kanamycin, a new antibiotic derived from *Streptomyces kanamyceticus*, was made available commercially in 1958. In July of that year, a symposium held at the New York Academy of Sciences included reports on the chemistry, pharmacology, microbiology, and clinical effects of this new antibiotic. These reports attested to its efficacy in the treatment of infections due to *Staphylococcus aureus*[1,2] and in gram-negative bacillary infections,[3] particularly the coliform group and some strains of the *Proteus* species. Less impressive results were indicated in the treatment of tuberculosis[4] with kanamycin. The oral preparation of this drug was reported[5] to be a satisfactory agent for bowel sterilization. Chemically, kanamycin resembles neomycin,[3] and the antibacterial spectrum and toxicity of these drugs are similar. Like neomycin, kanamycin is bactericidal.

*Associate in Medicine, Delaware Hospital.
**Senior Medical Resident, Delaware Hospital.
***Bacteriologist, Delaware Hospital.

The introduction of kanamycin is timely, because its effective spectrum includes organisms which have become resistant to many of the currently available agents. Kanamycin enjoys an advantage over the other antibiotics recently introduced for the treatment of resistant staphylococcal infections in that it may be administered intramuscularly. Although intramuscular injection is the preferred route, kanamycin has been administered intravenously to a number of patients in this hospital without local or systemic reaction. It has become necessary to alert physicians that the oral preparation of kanamycin should be utilized only for bowel sterilization, since there is minimal absorption of the drug through the gastro-intestinal tract.

The nephrotoxic and ototoxic effects of kanamycin were noted[6,7,8] at the symposium in New York. Subsequent reports[9,10] have stressed the ototoxicity of this drug, and this factor has been a deterrent to its wide-

spread systemic use. There is disagreement in the literature on the incidence of kanamycin-induced eighth nerve damage. Perhaps this difference depends on the intensity of the search for evidence of ototoxicity. As an example, Herrold and Karabatsos,[11] reporting on the use of kanamycin in urinary tract infections, stated that eighth nerve damage was not a problem, but no indication was given whether ototoxic evaluation was clinical or audiometric. It has been suggested in one paper[12] that, other than in lifesaving situations, kanamycin be relegated to topical use only, as has been neomycin. Nephrotoxicity from kanamycin has not been a problem, but it is evident that eighth nerve damage is more frequent and severe in the presence of impaired renal function.

An appreciation of the potential clinical value and the suspected toxicity of kanamycin prompted the Infectious Disease Group at the Delaware Hospital to undertake a limited evaluation of this new antibiotic. We believe that only through careful clinical experience can one properly appraise and utilize each new antibacterial agent. The following is a report of that experience.

CASE PRESENTATIONS

Thirty-six patients, ranging in age from 2 months to 80 years, were given kanamycin* in doses from 0.25 to 2.0 g. per day. Four of the patients were given kanamycin by the intravenous route; the remainder received the drug intramuscularly. A local burning sensation followed some intramuscular injections, but this did not require cessation of therapy. As mentioned above, there were no adverse reactions to the intravenous route.

Thirty-four of the 36 patients were treated in the Delaware Hospital; two of the patients were treated in the Memorial Hospital. Kanamycin was selected for patients in whom there was clinical or laboratory evidence that the antibiotic might be effective. As in any "new drug" study, several patients who were terminally ill from overwhelming infection not responding to mul-

*The kanamycin used in this study was supplied by Bristol Laboratories as Kantrex.

TABLE I

Infections of Urinary Tract

Case	Age	Sex	Diagnosis	Organism Source	Total Dosage	Response — Comment
1	48	F	Acute pyelitis	Pseudomonas	7.0 g.	Excellent—Organism sensitive to kanamycin
2	44	F	Recurrent pyelitis	E. coli	6.75 g.	Good—Subsequent relapse
3	17	F	Acute pyelitis	E. coli	13.0 g. 7 days	Good—Pregnant; with bacteremia also
4	28	F	Pyelonephritis	E. coli	9.0 g. 6 days	Good
5	61	M	Renal calculi	Paracolon	11.0 g.	Good—Drug used post-op.—Relapse
6	79	F	Renal calculi	Coliform	8.25 g. 7 days	Good—Hemiplegia, comatose—Reinfected
7	78	M	Obstructive uropathy	Paracolon	6.6 g. 6 days	Good—Diabetes, subsequent prostatectomy
8	70	M	Chronic infection	E. coli	8.25 g. 8 days	Good—Diabetes, indwelling catheter
9	77	M	Chronic infection	E. coli	11.5 g. 6 days	Good—Catheter, 8th nerve damage
10	44	F	Chronic pyelonephritis	E. coli	6.26 g. 7 days	Good—Blind—Now totally deaf
11	73	M	Obstructive uropathy	St. aureus and Paracolon	8.0 g. 6 days	Indeterminate—Urine cleared then relapse
12	67	M	Chronic cystitis	Enterococcus	5.0 g. 5 days	Poor—Catheter—8th nerve damage
13	66	M	Chronic cystitis	Klebsiella-Aerobacter	9.75 g. 7 days	Good—Catheter, staph. boil during treatment

tiple antibiotics were given this agent as a last resort. All of the 36 patients had pre- and post-treatment hemograms. Urinalyses were done every other day during therapy, and blood urea nitrogen determinations were carried out every third day. Appropriate cultures were obtained, and disc and test tube sensitivity tests were performed on all pathogens recovered. The anti-bacterial level of patient's serum (Schlichter titer) was determined in a majority of the cases. Audiologic consultation and follow-up was obtained in 13 of the 36 cases*. Tables I through IV summarize the results of treatment with kanamycin .

Cases 1 through 13 (reviewed in Table I) were suffering from urinary tract infection. The first four cases comprised acute uncomplicated urinary tract infection; the remaining nine had urinary tract infection complicated by obstruction or catheter. Designation of cases of urinary tract infection as either acute uncomplicated, or chronic with catheter or obstruction, is important in assessing results of therapy. In our experience, the uncomplicated infection can be easily eradicated with a variety of antimicrobial agents, while any treatment of chronic infection is usually unsatisfactory until the obstruction is relieved or the catheter removed.

The four acute infections all showed a good initial response to kanamycin therapy. Case 2 remained clinically well but had a bacteriologic relapse, *E. coli* again being isolated from the urine one week after therapy. A 17-year old pregnant girl (Case 3) with bacteremia complicating pyelonephritis was quite toxic but responded promptly to kanamycin (0.5 g. every 6 hours). This patient was known to have prior eighth nerve damage but showed no audiometric change during or after kanamycin therapy. The *Ps. aeruginosa* isolated from the urine of Case 1 is the most sensitive strain of this species we have encountered, being inhibited in the test tube by 3.1 mcg. per cc. of kanamycin. The clinical response was excellent.

Seven of the 9 obstruction or catheter cases had a good response in that the infecting organism was cleared from the urine; however, 3 cases relapsed, and in 3 others a cure depended on surgical relief of the

*The authors are indebted to Mr. L. L. Horne and Mr. D. M. Knapp of the Audiology Clinic, Delaware Hospital, for audiometric evaluation.

TABLE II

Postoperative Infections — Peritonitis

Case	Age	Sex	Diagnosis	Organism Source	Total Dosage	Response—Comment
14	67	M	Wound infection exfol. dermatitis	St. aureus—blood and wound	26 g. 20 days	Indeterminate—Pt. expired. Steroid therapy
15	55	M	Gangrene foot	St. aureus—wound	8.0 g. 8 days	Good—Wound not sterile
16	18	M	Cushings Disease with adrenalectomy	St. aureus—wound	13.0 g.	Good—Wound not sterile
17	24	M	Multiple fractures	St. aureus and Proteus—wound	26.0 g. 14 days	Poor—Clinical and bacteriological
18	58	M	Gastrectomy	Klebsiella—Aerobacter—wound	23.0 g. 14 days	Poor—No response to therapy
19	48	F	Neck dissection	St. aureus—wound	9.0 g. 7 days	Good—Afebrile 48 hours
20	82	M	Wound infection, pneumonia	St. aureus—wound	6.0 g. 3 days	Poor—Terminal when treatment started
21	2 mos.	M	Suprahepatic abscess	St. aureus—wound	1.4 g. 7 days	Good—Wound not sterile
22	12	M	Perforated appendix	E. coli—abdominal fluid	4.3 g. 5 days	Good—Clinical organism changed
23	53	F	Carcinomatosis, peritonitis	E. coli—abdominal fluid	10.0 g. 10 days	Indeterminate

obstruction or removal of the catheter. Case 10 became totally deaf following kanamycin therapy and will be discussed in detail below. Catheter cystitis improved in a 66-year old male (Case 13), but during kanamycin therapy he developed a large gluteal abcess from which a kanamycin-sensitive strain of *Staphylococcus aureus* was isolated.

Table II summarizes our experience with kanamycin in the treatment of patients with postoperative wound infections and/or peritonitis. Seven of the 10 patients in this group had infections due to *Staphylococcus aureus*. Four of the 7 were considered to show a good clinical response, although the organism was not eradicated from subsequent wound cultures. Three other patients with staphylococcus infection expired despite kanamycin therapy. It is difficult to evaluate the "effect" of kanamycin in these 3 cases; however, we considered the effect of the drug to be poor in one case and indeterminate in two cases. "Indeterminate" as a category was necessitated by (1) the utilization of a number of therapeutic measures which made it difficult to assess the effect of any one measure and (2) the tendency of administering newly introduced drugs to terminal cases as a "last-chance" measure.

A coliform bacillus was the infecting organism in each of the 3 remaining patients. A 12-year old boy with a perforated appendix (Case 22) experienced a good response. Twenty-three grams of kanamycin in 14 days failed to alter the course of a post-gastrectomy wound infection (Case 18) in a patient who subsequently expired. Case 23 also died of post-operative peritonitis complicating carcinomatosis. Kanamycin had no obvious effect on the course of the infection other than a temporary suppression of a high spiking fever.

The next group of cases (Table III) suffered infections of bone, skin, or the respiratory tract. Case 24 had chronic osteomyelitis due to *Staph aureus* and *Prot. mirabilis*. Kanamycin effected prompt improvement with cessation of drainage. The infecting organism was not obtained from another patient with osteomylitis (Case 25), and the response to kanamycin was indeterminate. A 5-year old girl (Case 26), critically ill with an abcess of the nasal septum, was given 3 g. of kanamycin over a 4-day period. This produced an excellent

TABLE III

Infections of Bone, Skin, Respiratory Tract

Case	Age	Sex	Diagnosis	Organism Source	Total Dosage	Response—Comment
24	40	M	Paraplegia, chronic osteo.	St. aureus and Proteus sp.—hip	20.0 g. 12 days	Good—Afebrile
25	63	F	Osteomyelitis	None	21.0 g. 14 days	Indeterminate—8th nerve damage
26	5	F	Abscess nasal septum	St. aureus—nose	3.0 g. 4 days	Good—Afebrile 24 hours—8th nerve
27	63	F	Cellulitis, leg	St. aureus—drainage	7.0 g. 7 days	Good—Culture not cleared
28	20	M	Hodgkins	St. albus—blood St. aureus—throat	5.25 g. 5 days	Good—Afebrile 24 hours
29	3	M	Bronchitis	St. aureus—nasopharynx	1.0 g. 5 days	Good—Afebrile
30	49	M	Bronchopneumonia, methyl alcohol	None	6.25 g. 4 days	Indeterminate
31	63	M	Lung abscess	Klebsiella—Aerobacter—sputum	15.0 g. 10 days	Indeterminate—8th nerve damage
32	54	M	Pneumonia	Klebsiella—Aerobacter—sputum and blood	15.0 g. 15 days	Good—Treated with streptomycin and tetracycline

response; but, on the fourth day of therapy, audiometric evaluation revealed kanamycin ototoxicity without conversational loss, although renal function was normal. Two patients with *Klebsiella-Aerobacter* pulmonary infection were treated with kanamycin (Cases 31 and 32). The first had a lung abcess from whose sputum a *Klebsiella* was repeatedly isolated. Kanamycin appeared to be exerting a benficial effect on the infection when audiometric evidence of eighth nerve damage necessitated cessation of therapy. The second case, acutely ill with *Klebsiella* pneumonia and septicemia, showed striking improvement when tetracycline-streptomycin was administered, but the fever persisted. Kanamycin was then substituted for the other antibiotics, with subsidence of fever and continued clinical improvement.

Septicemia complicated severe underlying disease in the 4 patients presented in Table IV. An 80-year old female (Case 33) underwent a cholecystoduodenostomy to by-pass a carcinoma of the head of the pancreas and became acutly ill on the eighth postoperative day with a temperature of 105° and a leukocytosis of 59,000. A gram-negative rod septicemia was suspected, and intravenous kanamycin was instituted immediately. Prompt clinical improvement occurred in spite of the isolation of a kanamycin-resistant pneumococcus type 14 from the blood culture (minimal inhibitory concentration—50 mcg. per cc.). It is significant that serum antibacterial activity during kanamycin therapy was adequate (Schlichter titer 1:4). This patient showed conversational hearing loss following therapy, although renal function was normal. Case 34, a 76-year old man, developed a coliform bacillus septicemia complicated by shock following urethral instrumentation. Intravenous kanamycin (0.5 g. every 8 hours) was instituted immediately, and the patient experienced a prompt response and became afebrile in 24 hours.

A patient with *Pseudomonas* septicemia complicating acute leukemia (Case 35) was treated unsuccessfully with a constant intravenous drip of kanamycin, for a total dose of 12 g. in 8 days. Cognizant of the fact that most strains of pseudomonads are resistant to kanamycin, we based our use of this drug on an excellent inhibition zone about the 30-mcg. kanamycin disc (utilized only because no 10-mcg. discs were available). Subsequent test tube dilution revealed the inhibitory concentration of kanamycin for this strain to be between 25 and 50 mcg. per cc. After 8 days of therapy, kanamycin was discontinued and a combination of streptomycin and tetracycline was given intravenously, with consequent rapid clinical improvement. Case 36, a 6-year old girl with leukemia and *Klebsiella-Aerobacter* septicemia showed no response to continuous intravenous kanamycin. Terminal invasion of the blood stream by strains of *Proteus* and *Pseudomonas* occurred during therapy.

TABLE IV

Infections of Blood Stream

Case	Age	Sex	Diagnosis	Organism Source	Total Dosage	Respose—Comment
33	80	F	Carcinoma pancreas	Pneumococcus Type 14	5.0 g. 4 days	Good—in vitro resistance, 1:4 Schlichter titer, diminution hearing
34	76	M	Prostatic hypertrophy	Klebsiella—Aerobacter	6.0 g. 4 days	Good—shock, I.V. kanamycin, afebrile 24 hours
35	34	F	Leukemia	Pseudomonas	12.0 g. 8 days	Poor—disc sensitivities off I.V. kanamycin, streptomycin, and tetracycline
36	6	F	Leukemia	Klebsiella—Aerobacter	5 5 g. 8 days	Poor—I.V. kanamycin. Superinfection with Proteus-Pseudo

TABLE V

In Vitro Studies — Test Tube Dilution

Minimal Inhibitory Concentration

(mcg. per cc.)

Organism	Number of Strains Tested	0.05-2.0	2.1-12.5	12.6-25	26-50	100 and over
Prot. mirabilis	18		8	6	3	1
Staph. aureus	15	3	10	2		
Klebsiella-Aerobacter	6	2	3		1	
E. coli	12		6	5	1	
Pseudomonas sp.	7		1	2	1	3
Paracolon sp.	1		1			
Pneumococcus	1				1	

IN VITRO STUDIES

The minimal inhibitory concentration of kanamycin for the 60 strains of bacteria isolated from the patients in this study was determined. The test tube dilution technic was used. Self-explanatory results are presented in Table V. Likewise, a total of 600 strains (including *Staph. aureus, E. coli, Klebsiella-Aerobacter, Proteus sp.,* and *Pseudomonas sp.*) have been tested for kanamycin sensitivity utilizing a 10-mcg. disc. By this method, 100 per cent of the strains of *E. coli* and *Klebsiella-Aerobacter* were susceptible, all but one of 200 strains of *Staph. aureus* were sensitive, while only 27 per cent of the strains of *Pseudomonas* showed a zone of inhibition. Ninety-eight per cent of the *Proteus* species isolated were reported as kanamycin-sensitive; in our experience,[13] however, disc sensitivities are unreliable when testing strains of *Protues sp.* because of their swarming tendency, so that test tube sensitivities should be carried out.

Kanamycin blood levels were not determined; however, in 28 of the patients, antibacterial activity of the serum (Schlichter titer) was determined one hour and four hours following kanamycin injection. The infecting organism from the patient was the test organism used in a two-fold dilution of that patient's serum. An inhibitory dilution of 1:2 or better was considered to represent adequate antibacterial activity.[14] Twenty-three of the 28 patients tested had adequate serum activity one hour following intramuscular injection, and 18 patients had adequate levels at both one-and four-hour intervals. There was excellent corre-

TABLE VI

Renal and Eighth Nerve Toxicity

	Kanamycin Dosage	
	Over 1.0 g. per day	1.0 g. per day or less
Increased BUN	0	1
Increased urinary albumin	0	0
Increased urinary cellular content	4	0
TOTAL RENAL DAMAGE 13.8%		
	Audiometer Determinations on 13 of 36 Patients	
Eighth nerve damage	3	2
Clinical deafness	1*	1
EIGHTH NERVE DAMAGE 46.1%		

*no audiometric determination

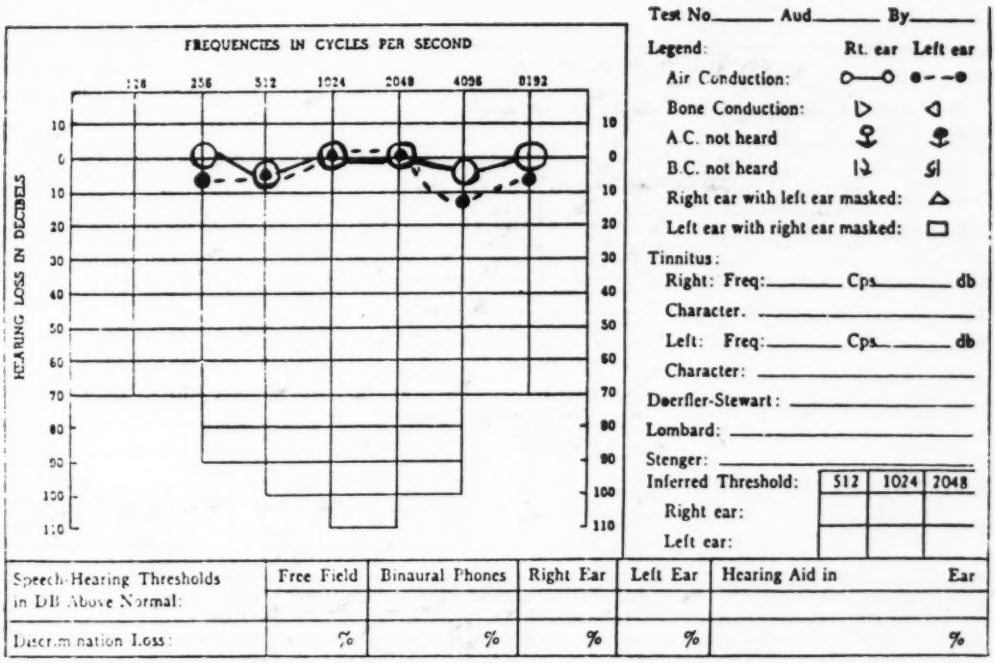


Figure 1. Audiometric Examination of January 15, 1959.

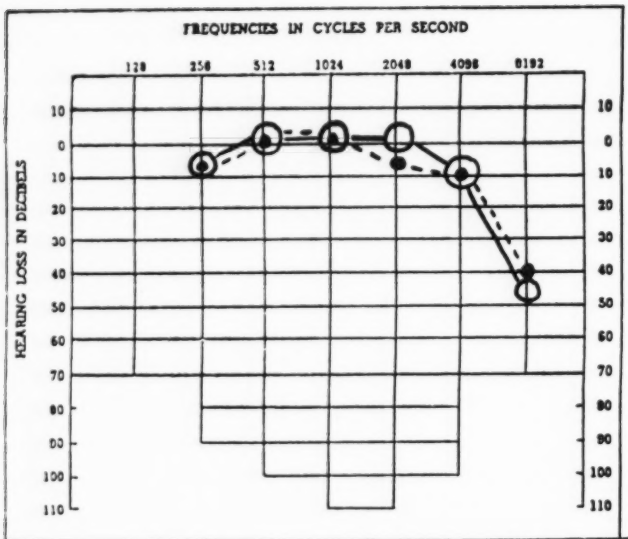
lation between serum antibacterial activity and successful clinical response.

Toxicity

Acute renal insufficiency concomitant with the administration of kanamycin has been reported,[6] but most reviews indicate a minor nephrotoxic role for this drug. Increase in urinary sediment has been the most common evidence of renal irritation.[3] Renal toxicity was uncommon in our experience—only 5 of 36 patients (13.8 per cent) giving clear-cut evidence of this complication. Four of the patients showed an increase in urinary cellular content while receiving more than one gram of kanamycin per day.

Only one patient (Case 10) had an increase in blood urea nitrogen (BUN), and she received less than one gram per day; however, there was slight elevation of BUN prior to therapy, due to longstanding kidney disease associated with hypertension. The BUN on the first day of therapy was 26 mg. per cent, and the audiogram (Fig. 1) was normal. We incorrectly surmised that the uremia was due in part to the chronic *E. coli* pyelonephritis, but on the fourth day of therapy the BUN was 49 mg. per cent, and the audiometric determination (Fig. 2) showed mild depression of high frequencies. On the seventh day of therapy, the BUN had risen to 68 mg. per cent, and the audiogram (Fig. 3) showed further hearing regression at 8000 cycles per second bilaterally. The audiologist concluded that kanamycin was affecting the eighth nerve, and the drug was discontinued. A post-treatment audiogram (Fig. 4) showed progressive damage; and at seven weeks following cessation of therapy, there was no usable hearing for communication — a tragic consequence, since this patient was totally blind. In retrospect, it is obvious that this patient should not have received kanamycin, and no patient should receive the drug until kidney function has been carefully evaluated.

Five of the 13 patients in this study who were subjected to audiometric evaluation showed definite evidence of eighth nerve damage (46.1 per cent). One additional



Test No.____ Aud.____ By____

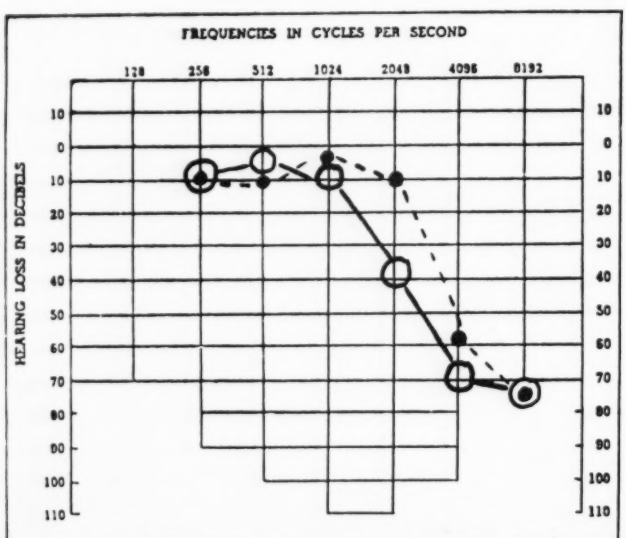
Legend:	Rt. ear	Left ear
Air Conduction:	o—o	•- -•
Bone Conduction:	▷	◁
A.C. not heard		
B.C. not heard		
Right ear with left ear masked:	△	
Left ear with right ear masked:		□

Tinnitus:
Right: Freq:____ Cps____ db
Character:____
Left: Freq:____ Cps____ db
Character:____
Doerfler-Stewart:____
Lombard:____
Stenger:____

Inferred Threshold:	512	1024	2048
Right ear:			
Left ear:			

Speech-Hearing Thresholds in DB Above Normal:	Free Field	Binaural Phones	Right Ear	Left Ear	Hearing Aid in Ear
Discrimination Loss:	%	%	%	%	%

Figure 2. Audiometric Examination of January 22, 1959.



Test No.____ Aud.____ By____

Legend:	Rt. ear	Left ear
Air Conduction:	o—o	•- -•
Bone Conduction:	▷	◁
A.C. not heard		
B.C. not heard		
Right ear with left ear masked:	△	
Left ear with right ear masked:		□

Tinnitus:
Right: Freq:____ Cps____ db
Character:____
Left: Freq:____ Cps____ db
Character:____
Doerfler-Stewart:____
Lombard:____
Stenger:____

Inferred Threshold:	512	1024	2048
Right ear:			
Left ear:			

Speech-Hearing Thresholds in DB Above Normal:	Free Field	Binaural Phones	Right Ear	Left Ear	Hearing Aid in Ear
Discrimination Loss:	%	%	%	%	%

Figure 3. Audiometric Examination of January 26, 1959

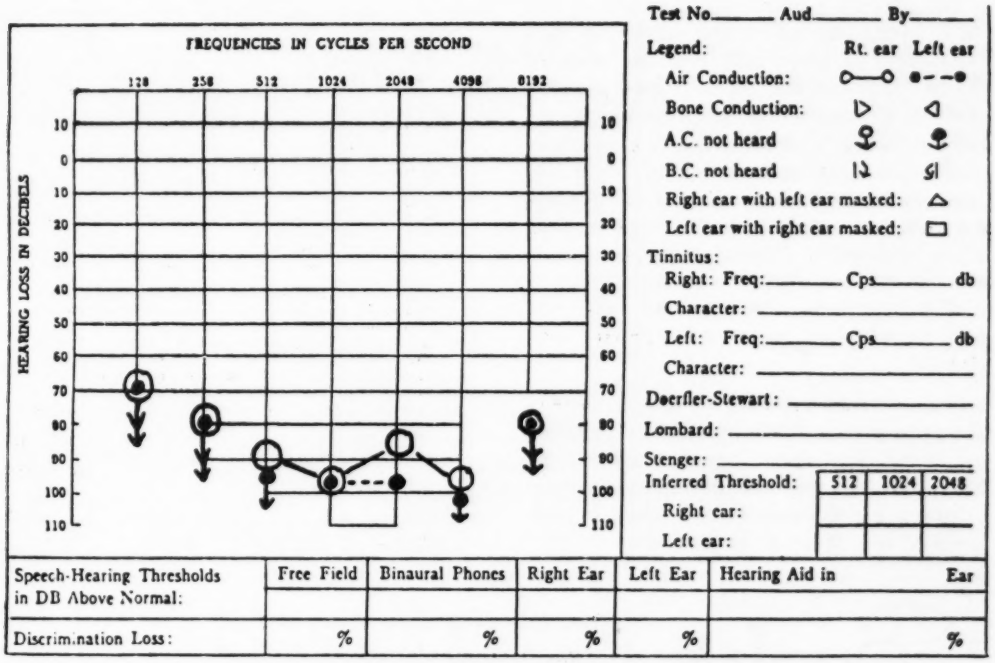


Figure 4. Audiometric Examination of March 10, 1959

patient developed obvious conversational deafness, although audiometric evaluation was not done. Except for the single case described above, renal impairment did not accompany eighth nerve damage in this study. Patients evaluated audiometrically were not selected but were dependent on the availability of the audiologist and the patients' own ability to cooperate.

Results

Table VII summarizes the results of therapy in the 36 patients treated with kanamycin. Two-thirds of these patients showed a favorable response.

Properly selected patients may be expected to benefit from therapy with this drug. If an antibiotic with the degree of toxicity manifested by kanamycin is to be used extensively, however, there must be clear-cut evidence that this agent is superior to one of already proven effectiveness against a specific infection. The reports

TABLE VII

36 Patients — Results of Therapy

Type of Infection	Good	Poor	Indeterminate
Acute urinary tract	4	0	0
Chronic urinary tract	7	1	1
Postoperative wound	4	3	1
Peritonitis	1	0	1
Osteomyelitis	1	0	1
Cellulitis	3	0	0
Respiratory tract	2	0	2
Blood stream	2	2	0
Total	24	6	6
	66.6%	33.3%	

in the literature and the experience in our study would lead one to the conclusion that kanamycin is frequently not the drug of choice. On occasion, we have seen patients presenting evidence of scepticemia of unknown etiology (probably due to a staphylococcus or coliform bacillus) in which we have used kanamycin initially with some assurance of clinical effectiveness against either organism. When subsequent bacteriological identification and susceptibility studies have been completed, we have then substituted other more appropriate antibiotics.

If no further evidence of the superiority of kanamycin is forthcoming, the systemic use of this drug should he relegated to carefully selected hospital patients in whom constant surveillance for evidence of ototoxicity can thereby be obtained.

REFERENCES

1. White, A., and Knight, V., Kanamycin: Pharmacological, microbiological and clinical observations. Ann. N. Y. Acad. Sci. 76: 289, 1958.
2. Yow, M., and Womack, G.: The use of kanamycin in staphylococcal epidemic in infants and children. Ibid. 76: 363, 1958.
3. Rutenburg, A., Koota, G., Schweinburg, F., The efficacy of kanamycin in the treatment of surgical infections. Ibid. 76: 348, 1958.
4. Donomae, I., Clinical studies of kanamycin treatment of pulmonary tuberculosis. Ibid. 76: 166, 1958.
5. Cohn, I., Kanamycin for bowel sterilization. Ibid. 76: 212, 1958.
6. Berman, L. B., and Katz, S., Kanamycin nephrotoxicity. Ibid. 76: 149, 1958.
7. Winfield, M., Crisp, G. O., Maxwell, M. H., Kleeman, C. R., Nephrotoxic effects of kanamycin: A preliminary report. Ibid. 76: 140, 1958.
8. Finegold, S. M., Winfield, M. E., Aronsohn, R. B., Hewett, W. L., and Guze, L. B., Clinical experience with kanamycin. Ibid. 76: 319, 1958.
9. Lecca, G. G., Terry, J., Maggiolo, L., Morales, A., Ototoxicity of kanamycin. J.A.M.A. 170: 2064, 1959.
10. Lustberg, A., and Hamburger, M., Eighth nerve deafness after administration of kanamycin. J.A.M.A. 170: 806, 1959.
11. Herrold, R. D., and Karabatsos, N., Effects of kanamycin on urinary infections. J. Urol. 82: 165, 1959.
12. Shambaugh, G. E., Derlacki, E. L., Harrison, W. H., House, H., House, W., Hildyard, V., Schubacht, H., and Shea, J. J., Dihydrosterptomycin deafness. J.A.M.A. 170: 1657, 1959.
13. Holloway, W. J., and Scott, E. G., Unpublished data.
14. Schlichter, J. G., MacLean, H., and Miller, A., Effective penicillin therapy in subacute bacterial endocarditis and other chronic infections. Am. J. Med. Sci. 217: 600, 1949.

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EVALUATION OF STAPES MOBILIZATION FOR OTOSCLEROSIS

● Stapes Mobilization, an operation discovered accidentally in 1952, has become a major factor in the alleviation of deafness due to otosclerosis. The author discusses the indications, contraindications and results of this proceeding and compares it with the fenestration operation.

HOWARD D. COHEN, M.D.*

Otosclerosis is the primary focal disease of the labyrinthine capsule that may in some cases invade the oval window causing fixation of the stapes, in other cases cause cochlear degeneration, or a combination of both. Improvement in hearing by surgery is possible in hearing loss due to otosclerotic stapes fixation, but not in hearing loss of cochlear origin. The selection of cases for surgery requires an accurate assessment of the conductive and perceptive components of the hearing loss in each patient with otosclerosis.[18]

Stapedial fixation was known in 1704, and it was shown in 1850[19] that, as a result of over one thousand postmortem examinations, stapedial footplate fixation was the cause of much deafness. Direct mobilization of the stapes was attempted in the period from 1876 to 1900, at which time the procedure was abandoned, and attempts were directed toward creating a new path way for sound to enter the inner ear, which led to the fenestra nov-ovalis operation of Lempert[11] in 1938 (fenestration of the horizontal semicircular canal). In 1952, Rosen performed a middle ear exploration in order to do a preliminary determination of the fixation of the stapes in a patient who was a candidate for the fenestration operation and he accidentally mobilized the stapes with restoration of hearing. He promptly informed otologists of his findings,[12] and as of May, 1958, over 25,000 stapes mobilizations or derivatives of the procedure had been performed in the U.S.

The history of a typical patient is one of progressive deafness with onset in the young or middle adult years in which the patient displays paracusis willisiana (the ability to hear better in a noisy environment), has a low volume or confidential voice, usually (about 50%) has a family history of a similar type of hearing loss, occasionally has increased hearing loss associated with pregnancy, has deprecusis[14] (inability to hear

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while chewing) and may have tinnitis and less frequently, vertigo of varying prominence in the history of the disease. A history of otalgia and or otorrhea indicates other ear disease, but in no way rules out otosclerosis with intercurrent infection. On examination, the tympanic membrane usually appears normal, but it may exhibit Schwartze's sign, a pink coloration. The Weber test will usually lateralize to the ear with the poorer hearing in this disease, the Rinne test will be negative, and the Schwabach test will be normal. Audiometry will show a hearing loss by air which is much greater than the loss by bone, which indicates that the nerve conduction or cochlear reserve is good.

Differential Diagnosis

The differential diagnosis in patients who partially fulfill the above criteria is as follows:

1. A phantom audiogram in a patient with unilateral perceptive deafness. This occurs when audiometric masking is inadequate, and sounds which are presented to the deafened ear are received by the good ear. This will give an air and bone conduction pure tone audiogram characteristic of otosclerosis, and tuning fork tests may well confirm this because the patient with a perceptively deafened ear has often lost the ability to localize sound. However, speech audiometry will not confirm the pure tone findings, and the diagnosis of otosclerosis should be viewed with suspicion. The erroneous diagnosis of otosclerosis is not uncommon.

2. Chronic adhesive otitis media. The history of infection may or may not be present, and the tympanic membrane may appear thickened and dull. The audiometric findings in this and in otosclerosis are similar, and the Gelle test is not capable of differentiating between the two conditions.

3. Disruption of the ossicular chain. This may be of congenital, postoperative, or traumatic origin. The history of the onset of deafness is usually, but not always, indicative of this condition. The audiometric findings are similar to those of otosclerosis, and the condition is amenable to surgical correction, either by performing a myringostapediopexy or by surgical restoration of the continuity of the ossicular chain.

4. Congenital fixation of the footplate. These patients have been deaf since birth, and the diagnosis can be established only by middle ear exploration.

The treatment of otosclerosis is such that hearing can be restored by the use of a hearing aid. Otosclerotic patients with a purely conductive hearing loss can achieve excellent hearing with the use of a hearing aid, but the use of a hearing aid may be compared to the use of a crutch. It will restore the ability to hear, but it will not restore normal hearing. For this reason, many patients with hearing loss have resorted to surgical correction of their conductive deafness, for which there are two operations to restore useful hearing, namely the fenestration operation and the stapes mobilization operation.

Fenestration Operation

The fenestration operation is a brilliantly conceived and executed bypass operation in which the sound conduction transformer action of the tympanic membrane and the ossicular chain are circumvented by the creation of a new pathway for sound pressure to stimulate the perilymphatic fluid, but it is necessary to concommitantly perform a radical mastoidectomy.

The stapes mobilization operation has as its surgical obective the adequate mobilization of the entire middle ear mechanism to transmit again the undistorted auditory vibrations to the perilymph with essentially normal amplitude.[6]

Various treatments which have been attempted to relieve otosclerotic deafness and which have failed include percussion and vibration applied to the short process of the malleus, exposure of the patient to various vapors, pneumomassage to the tympanic membrane applied externally, electromas-

sage, inflation of the Eustachian canal with air, stream or medicinal vapors, injection of fluid through the Eustachian canal, bougiennage of the Eustachian canal, electricity, and x-ray treatments.

A candidate for the stapes mobilization operation is any patient with otosclerosis who has no specific anatomic or pathologic contraindications, and who has a bone conduction not less than 45db, with a significant air-bone gap in the speech frequencies (500, 1000, and 2000 cycles).[6]

Goals of Stapes Mobilization Operation

The functional goals of the stapes mobilization operation are as follows:[13]

1. To obtain normal hearing (0-10db).
2. To restore hearing to an 11 to 20 db level in patients with some evidence of a perceptive loss in whom it is impossible to restore normal hearing.
3. To restore useful binaural hearing.
4. To remove the conductive component of a mixed hearing loss (perceptive and conductive).
5. To permit the successful use of a hearing aid in a patient with extreme deafness of a mixed type where a hearing aid alone cannot produce satisfactory hearing, but on whom the operation would not be expected to produce satisfactory hearing without aid.

The operation may also be considered to eliminate or reduce vertigo and tinnitis in a patient with otosclerosis who might not otherwise be considered a candidate for the operation.[3]

The preoperative audiometric classification of the patient's hearing loss has been established by the Otosclerosis Study Group.

The Class A patient has a hearing loss which is not greater than 10 db at 500, 1000, and 2000 c p s by bone conduction.

The Class B patient has a hearing loss which is not greater than 20 db at 500 and 1000 c p s and not greater than 30 db at 2000 c p s by bone conduction.

The Class C patient is one whose hearing loss does not fall into Class A or Class B.

There is no correlation between the age of the patient, the duration of the disease, or the severity of the hearing loss and the amount of improvement which can be obtained.

The operation is performed under local infiltration analgesia, and sedation is held to a minimum in order that the patient may respond to auditory stimuli so that the progress of mobilization can be determined. Most authorities employ a suspended, binocular, stereoscopic, variable magnification operating microscope with a self-contained source of illumination such as one manufactured by Carl Zeiss. The magnification and illumination provided by this instrument have been described as one of the most significant advances in stapes mobilization surgery.

The patient is placed in the dorsal recumbent position with the affected ear turned up, and after sterile preparation and infiltration analgesia, an incision is made in the posterior cutaneous external canal wall, and this wall is elevated from the osseus canal wall. This skin and the posterior half of the tympanic membrane are reflected forward over the anterior half of the drum exposing the tympanic cavity. It is usually necessary to remove some of the osseus external canal wall with a curette in order to expose the stapes and the oval window. The footplate of the stapes is inspected in order to determine the amount of otosclerotic involvement and the location of the otosclerosis in order to select the procedure which will best afford adequate mobilization.

Three Main Categories of Technique

The techniques employed to mobilize the stapes or achieve sound transmission to the perilymph are divided into three main catagories, namely the indirect methods, the direct methods, and the prosthetic implantations.

The first of the indirect methods to be used was that of Rosen which has been described as the "tilt" technique.[12] A curved mobilizer was placed on the neck of the stapes and an attempt was made to free the stapes with traction in a posterior direction. This method only provided about 35% good results, and about half the cases resulted in fracture of the stapes. The next development was the application of pressure in an inward direction with the pressure being applied either to the incus or to the head of the stapes, and these methods were known as the transincudial or transcapitular methods, but the percentage of good results was not improved materially over those obtained from the "tilt" method.

As the pathology is usually located at the circumference of the footplate, it was logical to transfer the efforts to break up the otosclerosis directly to the pathology, and thus the direct methods were developed. The otosclerotic foci were attacked either with a pointed instrument making multiple perforations, or with microchisels which cut directly through the otosclerosis. One author[1] postulated that in a successful mobilization by the tilt method, what actually occurred was a fracture through the anterior crus above the otosclerosis, and a fracture through the footplate behind the otosclerosis, maintaining continuity of the ossicular chain through the head of the stapes, the posterior crus, and the posterior half of the footplate. He devised an operation to create this condition in which he cut the anterior crus and cut the footplate across the middle, and this procedure was called a monopodal (one foot) lysis. When the otosclerosis was cut so that the entire footplate was freed and sound was transmitted through both crura, this was called a bipodal lysis.

The prosthetic implantations have been mainly polyethylene tubing, and some workers have recommended the use of tantalum wire. In cases where there is too much otosclerotic involvement at the margin of the footplate, or the entire footplate has too much involvement to prevent mobilization, a hole may be either picked or drilled in the footplate exposing the perilymph, and this is covered with a vein graft. A wire or polyethylene prosthesis is then inserted between the incus and the vein graft in order to maintain continuity of the ossicular chain. Results from the vein graft—polyethylene tubing operation have been encouraging.[16]

Most surgeons prefer to work directly at the footplate, and some will not hesitate to remove the crura of the stapes in order to mobilize or fenestrate a footplate which cannot be mobilized with the crura intact.

Complications Which Can Occur

Surgical complications which can impede or prevent the restoration of hearing are splitting or breaking of the long process of the incus, dislocation or avulsion of the incudostapedial joint, breaking or splitting of the head or neck of the stapes, fracture of one or both of the stapedial crura, annular ligament tear, dislocation of the stapes into the vestibule, facial nerve injury, chorda tympani nerve injury, and tympanic membrane perforations.

The stapes mobilization operation is not simple; it is a painstaking surgical procedure not without complications. It has been described[8] as an operation more difficult to perform than the classical fenestration, which is a radical mastoidectomy and fenestration of the horizonal semicircular canal. Among the postoperative complications which can occur are parotitis, otitis externa, tubotympanitis, facial paralysis, either temporary or permanent, loss of residual hearing, persistent tympanic membrane perforation, perverted taste sense, dead labyrinths, and mastoiditis. Two deaths are known of, but not reported, resulting directly from this operation. However, there has been much illogical criticism of the operation, and the complications and risks were emphasized beyond the limits of reasonable consideration.[9]

The Advantages

The advantages of this operation in com-

parison with the fenestration are as follows:

1. It can restore normal hearing (0-10 db level). This operation can eliminate the audiometric surgical deficit (close the air-bone gap) which the fenestration operation cannot do. There is a residual 15 to 25 db air-bone gap after the fenestration operation because of the elimination of the sound conduction transformer action of the tympanic membrane and the auditory ossicles. The fenestration can restore only usable, but not normal hearing.

2. The surgical morbidity is minimal. A great number of the patients are discharged from the hospital on the day following surgery, and the incidence of postoperative vertigo and nausea is reduced both quantitatively and qualitatively. The fenestration requires seven to ten days hospitalization, and vertigo is often severe for weeks.

3. The postoperative treatment required is usually minimal because the anatomy of the ear has not been altered, and the incision heals primarily. It often takes several months for the radical mastoidectomy cavity of the fenestration to heal, and about 13% of post-fenestration patients have a chronically draining ear. Weekly or semiweekly postoperative visits may be required after the fenestration for one to three months.

4. The ear of the patient is not disfigured by the stapes mobilization operation. There is no indication to the layman that an operation has been performed. Although the cosmetic appearance after the fenestration is quite acceptable, the radical mastoidectomy bowl of the fenestration is difficult if not impossible to fit with a hearing aid mold should the operation be unsuccessful.

5. No long term (life time) postoperative care is required; the fenestration must be seen semiannually or annually in order to maintain toilet of the cavity.

6. The incidence of persistent postoperative vertigo is low—0.3%.[5]

7. The stapes mobilization may be indicated for patients who would not be candidates for the fenestration operation because of either audiometric or medical contraindications.

8. Remobilization may be performed within six months after a previously unsuccessful mobilization attempt.[9]

9. An unsuccessful mobilization attempt does not statistically impair the chances of the patient to have a successful fenestration performed.[2]

10. Binaural hearing can often be reestablished with the stapes mobilization operation. Because of the difficult postoperative course after the fenestration, many patients with successful hearing restoration are reluctant to have a fenestration performed on the contralateral ear, but after the mobilization operation, most patients wish to have binaural hearing restored. The advantages of binaural hearing are[1] the ability to localize the source of a sound, the ability to hear well in a noisy environment, and the lowering of the speech reception threshold.

The Disadvantages

The disadvantages of the stapes mobilization operation are as follows:

1. It is not predictable. This is an early claim against the operation which is no longer true. As more experience has been gained, the percentage of successful operations has been reported to be between 65% and 80%. A recent report by a reliable author stated that 95% good results were obtained with his modification of the operation.[17]

2. The reankylosis rate is significant. This is true, but the rate is low, and if reankylosis occurs, revision of the mobilization or a prosthetic implantation can be performed. It has been suggested that if hearing improvement was maintained for at least one year, the operation should be considered as a worthwhile surgical procedure.[10]

The problem of the criteria for success of the operation is a difficult one, and these

criteria vary from author to author. Some recommend the use of the average of the three speech frequencies as measured by pure tone air conduction audiometry, while others recommend the use of the Fletcher equivalent speech reception threshold, which is an average of the best two of the three speech frequencies. This has been claimed to more closely approximate the level of hearing which the patient exhibits, and it may be slightly higher than the average of the three speech frequencies. Another recommendation is to use only the speech reception threshold as tested with the speech audiometer.

Some patients are considered to be improved if their hearing reaches the 35db level, while other groups require that the hearing must reach the 30db level before the patient can be considered improved. This is a satisfactory way to evaluate the Class A and the Class B patients, but not many of the Class C. patients could be regarded as successful under these criteria. A conductive efficiency evaluation[7] was proposed which is the ratio of the postoperative gain divided by the maximum predictable gain, and this is expressed as a percentage. This is a good way to express the success of the operation, but it does not indicate the ability of the patient to hear.

PRESENTATION OF CASES

A series of twenty-four consecutive ears in seventeen patients is presented. All but one of these ears were operated upon by the author, either alone or under supervision. The one exception is an ear operated upon by John J. Shea, Jr., who demonstrated his vein graft and polyethylene prosthetic stapes operation on a patient whose contralateral ear is included in the series. The youngest patient was 31 years old, and the oldest patient was 69 years old. The medium age was 41 years. The sex ratio was 6 males and 11 females, 35% to 65%. There was one remobilization performed in this series, but no ear was operated twice.

Although this series is not large enough to be significant, the statistics obtained show trends that are in agreement with those presented by other authors. The period of follow-up study is too short to be significant. The longest followed patient was 16 months postoperatively. Most patients were followed at least 4 months. Interestingly, several patients who had a good result two weeks postoperatively often had a further marked gain when tested after two months.

TABLE 1

Total number of cases - 24 ears in 17 patients		
No. of "A" cases	5 "	21%
" " "B" "	8 "	33%
" " "C" "	11 "	46%
No. of ears achieving 30 db level or better	16/24	67%
" " "A" " " " " " "	5/5	100%
" " "B" " " " " " "	6/8	75%
" " "C" " " " " " "	5/11	45%
No. of ears achieving 20 db level or better	11/24	46%
" " "A" " " " " " "	5/5	100%
" " "B" " " " " " "	4/8	50%
" " "C" " " " " " "	2/11	18%
No. of ears achieving 10 db level or better	3/24	13%
" " "A" " " " " " "	0	0
" " "B" " " " " " "	2/8	25%
" " "C" " " " " " "	1/11	9%

Thirteen of these ears were operated upon employing the indirect method. They were either operated on at a time before direct methods were being used, or when indirect methods were attempted, and direct methods were employed only if the indirect attempts were unsuccessful. One patient had a footplate fenestration, vein graft, and prosthetic columella inserted between the vein graft and the incus with a good result. Toward the end of the series only direct methods were employed; these patients seemed to show better results, but the series is too small for analysis.

Two patients were admitted with the chief complaint of vertigo. Both patients received good hearing results, and one was

completely relieved of his vertigo. His case was described in a separate paper.[3]

Results

Two ears (80%) had a postoperative decrease in air conduction, but none was greater than 8db.

Four ears (17%) had a postoperative decrease in bone conduction, three of which were slightly greater than 10db, but two of the last mentioned three had an excellent increase in air conduction and are among the successful cases.

Ten of the sixteen successfully mobilized cases had an increase in the air conduction level almost to or above the pre-operative bone conduction level. The conductive efficiency evaluation was near or above 100% in these ten cases, and six were well above 100% (132-170%).

Summary

A brief description of otosclerosis and its diagnosis and treatment has been given. The advantages, disadvantages, and the complications of the stapes mobilization operation have been discussed. A series of twenty-four cases was presented.

Conclusions

The stapes mobilization operation is the surgical approach of choice for patients with clinical otosclerosis. It can restore hearing to a normal level (0-10 db), and it offers the patient the minimum of discomfort and morbidity. Conceivably, surgical skill will arrive at a level at which the only patients who cannot have surgical restoration of hearing by this method and its modifications are those whose fossa ovalis is so contracted that it is impossible to expose the oval window without injury to the facial nerve.

References

1. Bergman, M.: Binaural hearing. A.M.A. Archives of Otolaryngology 66: 572 (Nov.) 1957.
2. Campbell, E. H.: Stapes mobilization. A.M.A. Archives of Otolar. 68: 663-72 (Dec.) 1958.
3. Cohen, H. D.: Relief of vertigo by stapes mobilization in a patient with otosclerosis. A.M.A. Archives of Atolar. 70: 371-2 (Sept.) 1959.
4. Fowler, E. P., Jr.: Anterior crurotomy and mobilization of the ankylosed stapes footplate; introduction to a motion picture demonstration. Acta Otolaryngologica 46: 319-22 (July-Aug.) 1956.
5. Fowler, E. P., Jr.: In Symposium (Stapes Mobilization Two Years Later.) Laryngoscope 68: 1403-42 (Aug.) 1958.
6. Goodhill, V. & Holcomb, A. L.: A study of 500 stapes mobilizations. Laryngoscope 67: 615-42 (July) 1957.
7. Goodhill, V.: Stapes mobilization for otosclerotic deafness; the monitored peribasal technic. California Medicine 88: 114-22 (Feb.) 1958.
8. Juers, A. L.: Clinical otosclerosis — fenestration or stapes mobilization. J. Kentucky State Medical Asso. 54: 1056-8 (Dec.) 1956.
9. Kos, C. M.: Conservation of hearing; fenestration or stapes mobilization. J.A.M.A. 163: 814-817, Mar. 9, 1957.
10. Kos, C. M.: Mobilization of the stapes for improvement in defects in hearing due to clinical otosclerosis. J. International College of Surgeons 27(5) Part 1: 627-639 (May) 1957.
11. Lempert, J.: Improvement of hearing in cases of otosclerosis. A new one stage surgical technic. A.M.A. Archives of Otolar. 28: 42-97 (Jan.) 1938.
12. Rosen, S.: Palpation of the stapes for fixation; preliminary procedure to determine fenestration suitability in otosclerosis. A.M.A. Archives of Otolar. 56: 610-615 (Dec.) 1952.
13. Rosen, S. & Bergman, M.: Functional goals in mobilization of the stapes (with reference to hearing restoration). A.M.A. Archives of Otolar. 63: 11-20 (Jan.) 1956.
14. Scheer, A. A.: A new diagnostic sign of otosclerosis. A.M.A. Archives of Otolar. 69: 712-713 (June) 1959.
15. Schuknecht, H. F. et al: Results with chisels in Stapes mobilization. Laryngoscope 68: 726-740 (Apr.) 1958.
16. Shea, J. J., Jr.: Fenestration of the oval window. Annals of Otology, Rhinology and Laryngology 67: 932-952 (Dec.) 1958.
17. Shea, J. J. Jr.: Transactions of the American Academy of Ophthalmology and Otolaryngology: 1959 Meeting.
18. Shambaugh, G. E., Jr.: "Surgery of the Ear." W. B. Saunders Co. Philadelphia, Pa. 1959.
19. Toynbee, J.: On ankylosis of the stapes to the fenestra ovalis, etc. 1000 dissections. Proceedings of the Royal Medical and Chirugical Society of London 2: 63, 1858.

A.M.A. Fifty Year Club

Dr. J. H. McCurry, of Cash, Ark., advises that he has the approval of the American Medical Association to organize a Fifty Year Club within the AMA. Dr. McCurry is anxious to hear from physicians who have been in practice fifty years or more who desire to become members of this club, giving their name and a complete address.

The first meeting is to be held in Washington, D.C. at the Clincial meeting November 29 to December 2, 1960.

● It may seem that advising and performing rhinoplasty is to both the surgeon and the patient somewhat like playing with a loaded gun, but when advised and applied under careful conditions of selection, conception, and execution, rhinoplasty remains today, as in 1898, one of the most gratifying of all cosmetic operations.

FAILURES IN RHINOPLASTY

JAMES T. METZGER, M.D.*

With an increasingly popular acceptance of cosmetic surgery in principle, there has been a natural rise in the number of operations which are designed purely for an improvement in appearance, and which have little or no value in a functional sense. Although in the spectrum of plastic surgical procedures, operations of this type remain small in the total percentage of cases done, they do, nevertheless, play an important role in modern surgery.

Today's surgical literature is filled with descriptions of the technique of scar revision,[11] augmentation and reduction mammaplasty,[7] and face lifts.[16] Hardly a month goes by without discussion of some aspect of rhinoplasty, undoubtedly the most common cosmetic operation of all. Unfortunately this fact has led to frequent and often inaccurate accounts of its technique and merits in the lay press. Formerly an operation for the movie star, rhinoplasty is now available to the housewife as well. At clubs and teas, the results of different rhinoplasties are compared and criticized almost as one might compare and criticize a suit of clothes or a dress.

The scientific literature has been quick to describe the techniques of rhinoplasty—the general public has been quick to criticize and emphasize the faults in it. Neither has been particularly careful to appreciate or understand why the operation is not always completely successful. Of course, there have been, from time to time, good discussions on this point.[5, 12, 14] It still remains advantageous, however, to all who advise, receive, and perform rhinoplasty to see how there can be failures, and how these failures come about.

Basically, rhinoplasty achieves its purpose by remodeling three key areas of the nose: the dorsal line, the nasal base, and the nasal tip. The upper nasal pyramid is bony, and is remodeled both at the dorsum and base by a combination of fracturing, withdrawing and repositioning bone. The lower nasal pyramid is cartilaginous and is adjusted by freeing and trimming the septal and lateral cartilages.

The classic description of cosmetic rhinoplasty was by Jacques Joseph of Berlin in 1898[10] and excellent expositions on his work[9, 1, 3, 15] have continually improved the technique. Under optimum peacetime conditions, 72 hours of hospitalization and a major operating room set-up are required. Approximately 14 days of after care is necessary and, because of post operative blepheral edema and ecchymosis, most

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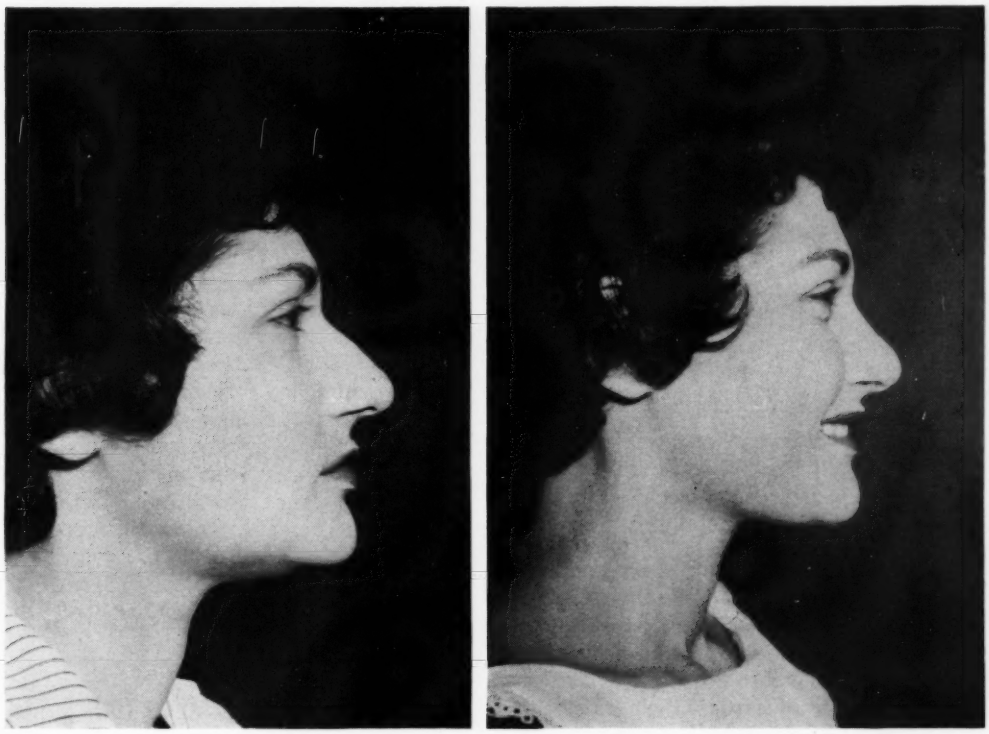

Figure I.

working people allow two full weeks before returning to their usual occupation.

Among plastic surgeons, local anesthesia has found wide acceptance.[13] This allows for normal tone and mobility of the face during the operation, which is a most helpful adjunct to on-the-spot evaluation and adjustment of nasal contours. Heavy preoperative sedation and accurate nerve block anesthesia make the operation painless and the recollection of it foggy.

The procedure is performed entirely from within the nose. Through bilateral internal alar incisions the bony dorsum is undermined. Laterally, this is subperiosteal, while over the hump it is subcutaneous. Bleeding is minimal. Bilateral internal alar incisions are then made and are joined at the apex of the vestibule by a transfixing columellar incision. Through this the nasal tip is undermined subcutaneously, and the undermining is carried upward until the entire cutaneous attachments are thoroughly released. The lower lateral (alar) catilages are dissected free and presented through their respective airways. The upper lateral cartilages are separated from the nasal septum so that the bony and cartilaginous septum stands free. Using either scissors or the No. 11 blade, the cartilaginous hump is cut through, and, using this cut as a guide, the bony hump is removed with the 5 millimeter osteotome. The entire bony and cartilaginous hump is then withdrawn, making the first major change.

A section of the medial portion of the lateral crus of the lower lateral cartilage is removed to narrow the nasal tip, and, if desired, a section adjacent to the upper lateral cartilages is resected to elevate the alar wing. At this stage, a portion of the maxillary nasal spine may be removed to increase the vertical height of the upper lip, and to sharpen the columellar angle.

The upper lateral nasal cartilages are trimmed of their redundancy and, using the guarded osteotome, the maxillary nasal processes are fractured free, flush with the face, thereby mobilizing the bony dorsum, which is set into its new positon. With the application of a dental compound splint, the operation is brought to a close. Rarely is it necessary to suture the original wounds, but, if so, this can be done with fine surgical gut. Position of the splint is maintained for about 48 hours, and subsequent taping is used until edema and ecchymosis have subsided.

There are, of course, individual variations in the technique as described, but these are usually minor. How then, in such a well established, time-tested, carefully described operation, can failures arise?

The answer is both simple and complex. Failures (simply) must sometimes follow when dealing with any situation in which there are many variables. And they arise (complexly) when these variables exist without an awareness of their existence and where they are subject to incomplete control.

In rhinoplasty, failure commonly follows when the patient does not appreciate the technical limitations of the operation. A human nose cannot be modeled as wood or clay. Nor is a surgical operation artistic to the degree that one can erase and change as with paper and canvas. A clear understanding on this point between patient and surgeon is essential. At the time of the first interview, it must be well understood that the surgeon can only alter the objectionable features of the nose, and that the result which follows this alteration will be an improvement on the original. He can never guarantee, either by expression or implication, that the alteration will match any preconception on the part of the patient.

Preoperative casts, drawings, or photographs which may be used to demonstrate what the patient will look like following rhinoplasty, may be seriously misleading. The surgeon can, however, extend reasonable assurance that, with correction of certain succinct disagreeable aspects of the nasal contour, an agreeable change will take place.

If there are limitations in the technique, there are also limitations in the technician —for at the operating table, the surgeon becomes this. The rate of failure in rhinoplasty will obviously relate to the training and experience of the operating surgeon. Over the years, there have been serious and exhaustive efforts to resolve the contours and planes of the face into some type of readily usable mathematical formula.[4] Expositions of the most careful type have studied the nose in relation to the face, as expressed in classic painting.[8] Straith[18] devised an instrument, which he called the "profilometer," as an aid in appreciation of nasal angles in relation to the face. But, aside from an artistic appreciation of what should be altered, the ability to perform these alterations accurately presents a most difficult surgical exercise.

Proper and clean osteotomies of the bony hump and nasal base are often difficult to attain; equal adjustment of the alar cartilages is essential; a smooth blend from the bony to the cartilaginous dorsum requires careful inspection of the junction of the two; and an equal in-fracture of the lateral nasal process must be done. The nasal septum is frequently twisted so that some degree of septum reconstruction, after the technique of Metzenbaum or Steffensen, is usually necessary. Every possible variable in the complex structure must be accurately controlled, making rhinoplasty truly surgery of millimeters. The surgeon also finds himself in the particularly difficult position of projecting, by way of the sensory advice of his fingers (for after separation of the nasal skin, visual appraisal is essentially valueless) what change he has been able to effect and imagine clearly what the ultimate resolution will be. This he must do in spite of vagaries in healing, callus formation, contractures, and even possible traumatic indiscretions by the patient.

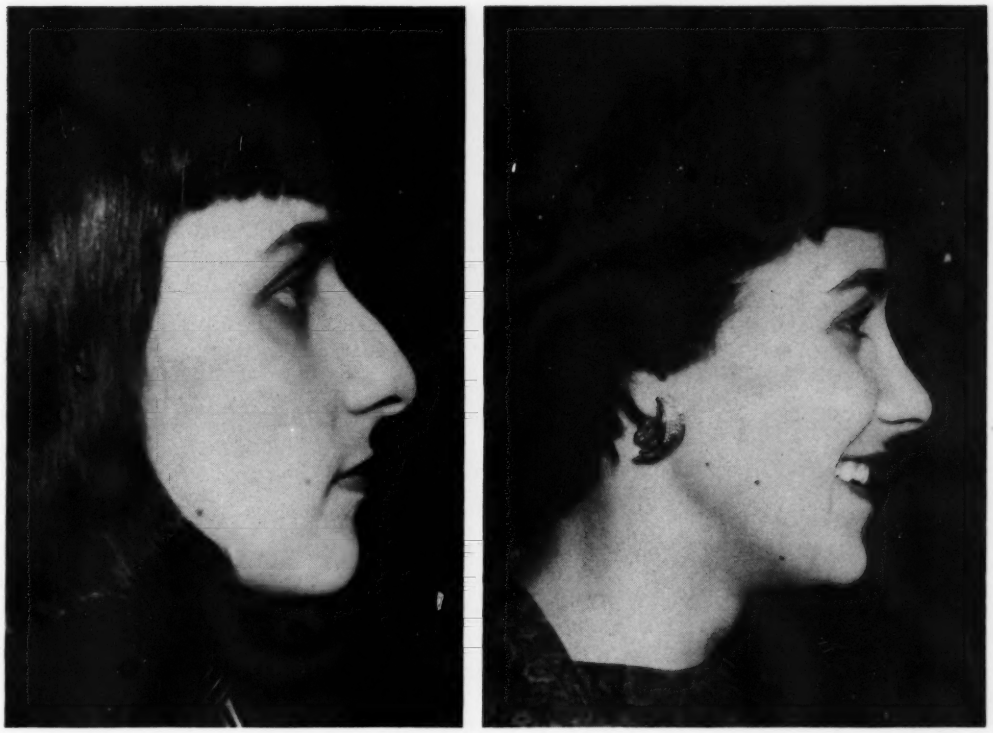

Figure 2.

The period of postoperative resolution is lengthy, not less than three months, and often extending up to a year. During this time, the initial result, which will be an improvement over the preoperative nose, will gradually become even better. During maturation, the skin, which is tense and firm, gradually softens, the "wooden" feeling of the nasal tip is replaced by normal plasticity, and cutaneous adhesions, which may indent the alar wing or dorsum, soften and fade. Both patient and surgeon need patience and understanding at this time, for it is during this period that casual remarks by friends may suggest to the patient that the rhinoplasty is a failure.

Although described above as a technician, any surgeon and particularly the rhinoplasty surgeon must be much more than that. Accurate appraisals and judgments must be made from beginning to end. An outstanding rhinoplasty surgeon has said[2] " . . . (the) esthetic sense can be developed with training and experience if there is an inborn foundation for it; if not, it is as futile as attempting to make a musician of one who is tone deaf." Failures with rhinoplasty thereby may follow a poor selection of anatomic types. Unless the nose is the dominent disharmonious feature of an otherwise pleasing face, rhinoplasty cannot hope to effect a fully satisfying change, and may, in fact, fashion an oddly curious countenance and thereby perform a genuine disservice.

Often skillful rhinoplasty surgeons find their work increasingly restricted to rhinoplasty alone. Gradually and inevitably, unless particular care is taken against this insidious attack, each nose begins to look somewhat like its predecessor. Each beautiful, but not in harmony with its owner's face. This, too, constitutes failure. If there is, to the casual observer, a clue that

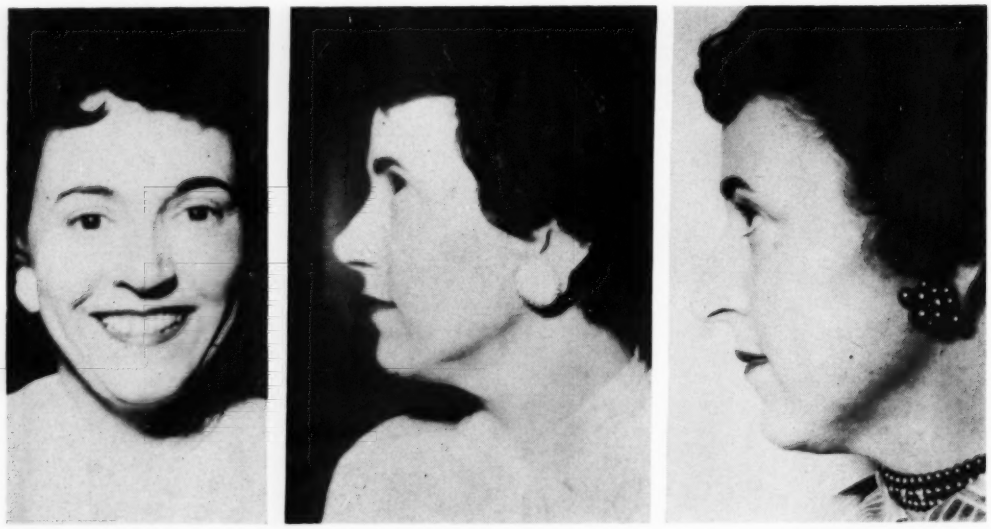

Figure 3.

a rhinoplasty has been done, the operation is less than a total success. The postoperative rhinoplasty should look, feel and perform as if it were the patient's own original nose. One nose will not fit another's face, each must *belong*.

Figure I illustrates the result following the reduction of a generally gross nose having no predominant preoperative deformity. The alar rims have been lifted to give more columellar exposure, and the total nasal pyramid has been reduced by about one-third. This has the secondary effect of appearing to reduce the cheek mass, elevate the forehead, and soften the chin line.

Figure 2 presents a reduced hump nose, which originally led into a bulbous and dependent nasal tip. The face is generally softened. All features appear more delicate, and a pleasing, youthful face results.

Figure 3 also demonstrates the rejuvenation possibilities in rhinoplasty. The long, droopy tip has been elevated and the dorsal line reduced. Again the optical illusion of advancement of the chin is evident. In these illustrations, the psychological impact to each individual cannot be projected. The tides of personal response perhaps reflect in the smiles of the postoperative photographs, but their depths are poorly understood.

It has long been recognized that the nose constitutes a prime sexual symbol.[17] To the surgeon, the complexity of this machination remains a mystery. Herein lies the most serious cause of failure in rhinoplasty. Nothing can be more distressing to patient and surgeon alike than a failure to appreciate preoperatively that a rhinoplasty is not what is required. Rather an extensive psychologic, if not psychiatric, readjustment may be what is essential. A patient with a beautiful rhinoplasty may constitute a miserable failure because of this. Rhinoplasty can change a nose, but not a way of life. Unfortunately, each of us considers himself well adjusted. One's work and social record may seem to bear this out, and it is not until a cosmetic rhinoplasty has failed to effect the result desired by the patient that it becomes belatedly apparent that subconscious desires have prompted the original call for help. Then, by his well meaning, although indiscreet efforts, the surgeon adds to, rather than subtracts from the patient's inner torment. When this unfortunate situation can

be detected in advance, a psychiatric consultation has been of extreme value and, although occasionally misleading, it can lend support and expert confirmation on a dubious candidate.[3, 6]

Perhaps this discussion has led to the conclusion that advising and performing rhinoplasty is to both the surgeon and patient somewhat like playing with a loaded gun—and to some degree, this is perhaps true—yet really not, for when advised and applied under careful conditions of selection, conception, and execution, rhinoplasty remains today, as in 1898, one of the most gratifying of all cosmetic operations.

REFERENCES

1. Aufricht, Gustave: A Few Hints and Surgical Details in Rhinoplasty. Laryngoscope 53: 317, 1943.
2. Aufricht, Gustave: personal communication.
3. Brown, James B. and McDowell, Frank: Plastic Surgery of the Nose. St. Louis, C. V. Mosby Co., 1951.
4. Caltagirone, J. V. and Kostecki, J. L.: The Face in Greek and Roman Art. Plas. and Recon. Surg. 15: 165, 1955.
5. Cohen, Samuel: Operative Complications of Rhinoplasty. Plas. and Recon. Surg. 17: 463, 1956.
6. Erich, John B.: The Selection of Patients for Rhinoplasty. Surg. Gyn. and Obst. 106: 481, 1958.
7. Gillies, H. and Millard, R. D.: The Principles and Art of Plastic Surgery. Boston, Little, Brown and Co., 1957.
8. Hay, D. R.: On the Science of Those Proportions by which the Human Head and Countenance as Represented in Works of Ancient Greek Art are Distinguished from those of Ordinary Nature. Edinburgh and London, 1849.
9. Joseph, Jacques: Nasenplastik und Sonstige Gesichtsplastick. Leipzig, C. Kabitsch, 1931.
10. Joseph Jacques: Surgical Correction of the Nose. Berlin. klin. Woch. 40: 882, 1808.
11. Metzger, James T.: The Cosmetic Closure of Simple Lacerations. Del. State Med. J. 29: 255, 1957.
12. O'Conner, G. B. and McGregor, M. W.: Secondary Rhinoplasties: Their Cause and Prevention. Plas. and Recon. Surg. 15: 404, 1955.
13. Pickrell, Kenneth L.: Nasal Deformities and Their Repair. Surgery 20: 845, 1946.
14. Safian, Joseph: Failures in Rhinoplastic Surgery. Am. J. Surg. 50: 274, 1940.
15. Safian, Joseph: Corrective Rhinoplastic Surgery. New York, Paul Hoeber Co., 1935.
16. Smith, Ferris: Plastic and Reconstructive Surgery. Philadelphia, W. B. Saunders Co., 1950.
17. Strahan, Charles: personal communication.
18. Straith, C. L.: Reconstruction About the Nasal Tip. Am. J. Surg. 43: 223, 1939.

MANIFESTATIONS OF COXSACKIE GROUP B INFECTIONS IN CHILDREN

WITH SPECIAL REFERENCE TO VARIOUS TYPE 5 ENTITIES

● The case reports of three children with Coxsackie Group B, infection are presented. The first, simulated aseptic meningitis; the second, non-paralytic poliomyelitis; and the third had only rapidly subsiding fever, chills and muscular cramps. The author shows that one particular virus can cause a wide spectrum of illness creating a dilemma wherein the physician must distinguish between a bacterial or virus infection and decide to treat or not to treat with an antibiotic.

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The purpose of this paper is two-fold:

1) A review of part of the literature concerning Coxsackie Group B infections in children; and
2) To report on the varied clinical signs and symptoms seen with infections caused by the Coxsackie B Type 5 virus specifically.

Three pediatric patients were seen in the summer of 1958 during a month's interval with varying manifestations of disease which are felt to be attributable to this one particular virus (Coxsackie type B-5) on the basis of serological and/or isolation findings.

GENERAL COXSACKIE VIRAL INFECTIONS

Dalldorf and Sickles in 1948 were the first to isolate the Coxsackie virus.[1] In their original paper they described a poliomyelitis-like illness in a nine year old boy who seven months later still was unable to sit up from a recumbent position because of truncal muscle weakness, although the weakness of other muscles had disappeared. Their second case concerned a three and one-half year old boy who had weakness of his abductors and inversion of his left foot when walking six weeks after his initial illness; he subsequently recovered completely. By appropriate cultural and serological means, they were able to demonstrate the existence of this new agent and its ability to cause clinical infection in man.

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Divided Into Two Main Groups

Since this original identification, much investigative work has been done regarding disease entities caused by Coxsackie virus infections. It has been well established that they can cause herpangina, epidemic pleurodynia (seen mostly in the adult age group), encephalitis, aseptic meningitis, and myocarditis.[2]

As of 1955, Dalldorf divided the Coxsackie viruses into two main groups: those

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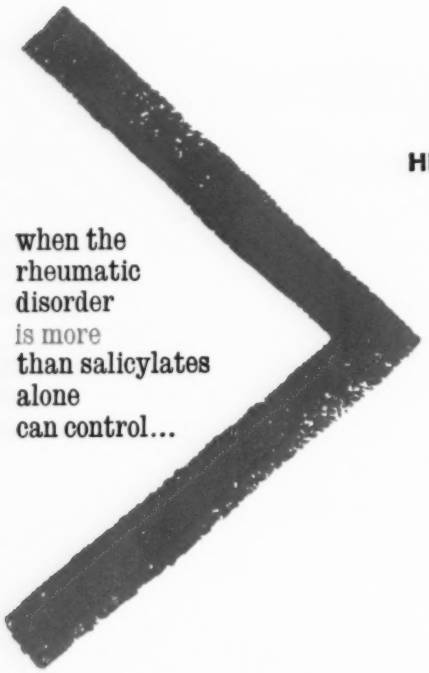

when the
rheumatic
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HIGHLY INDIVIDUALIZED
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agents producing predominantly skeletal-muscle inflammation in the mouse fell into group A; those agents causing changes in other organs, such as the brain, pancreas, fat pads (as well as muscle to a lesser degree) fell into group B.[3] Parrot, likewise, states that "group A Coxsackie viruses are those which produce paralysis and marked degeneration in muscle but no significant lesions in the central nervous system in suckling mice, and cause no apparent disease in adult mice. Group B Coxsackie viruses tend to cause encephalomyelitis, focal myositis, pancreatitis and fat necrosis. Clinically, group A viruses are associated with herpangina and the group B virus is associated with pleurodynia and aseptic meningitis."[4] This basis for division of Coxsackie viruses into group A and group B is also the feeling of Kibrick and Benirschke.[5]

Early Reports

There are many reports in the literature of the disease entities caused by the Coxsackie group B viruses. McLeod and his associates reported on a study of seventeen cases of aseptic meningitis caused by Coxsackie B viruses, adequately evaluated to exclude a concurrent infection with polio-virus.[6] The main clinical features of these cases of aseptic meningitis were pyrexia, signs of nuchal irritation, nausea and vomiting, headache, drowsiness, and myalgia. Not one of their cases developed paralysis or residual muscular weakness. Examination of the cerebrospinal fluid revealed a pleocytosis of between eleven to five hundred white blood cells per cubic millimeter. The average white blood count per cubic millimeter was one hundred and seventy-one, and the cerebrospinal fluid protein was usually normal or slightly elevated. The strains isolated in their study were Coxsackie group B_1, B_2 and B_4.

Likewise, Javett and his group described an outbreak in a maternity home in Johannesburg in which a number of newborn babies became ill while in, or soon after discharge from, the particular maternity home in which they were born.[7] This outbreak occurred in October and November of 1952 at a time when epidemic pleurodynia (Bornholm disease) was quite prevalent. The age of onset of the disease varied from five to seventeen days of life; and of the ten babies so afflicted, six died. Postmortem study showed a patchy myocarditis and foci of encephalitis. Bacteriological studies were negative and the illnesses were felt to be related to the Coxsackie group B viruses.

Neonatal Cases Serious

Coxsackie group B virus infections are of much more serious consequence in the neonatal period it would seem. Hosier and Newton reported on the isolation of a Coxsackie group B type 4 virus from the myocardium of a seven week old infant who died in heart failure, and from the myocardium, liver, lungs and kidney of a fourteen day old infant who died of sepsis of unknown cause.[8] They also recorded the history of a five year old boy admitted in heart failure who recovered completely from myocarditis, as evidenced by electrocardiographic changes, during which time group B type 2 Coxsackie virus was isolated from the stool of the child with a subsequent rise of the homologous serum neutralizing antibodies. This latter child was treated with steroids.

The fourteen day old infant also showed extensive focal necrosis of the liver (she was clinically jaundiced), a mild meningoencephalitis and a focal necrotizing infection of the adrenals. The first two cases reported above brought the total to twelve of infants reported to have died with myocarditis associated with a group B Coxsackie virus at that time. Noteworthy was the author's comment that the seven week old child was the eldest to have died of proven Coxsackie viral myocarditis at that time. Furthermore, of the twelve cases reported up until that time, fifty per cent showed involvement of the central nervous system and thirty-three per cent showed changes in the liver consistent with those produced by other viruses. Likewise, sixteen per cent showed adrenal involvement; and, thus the authors feel that Coxsackie

group B virus infections can be systemic, similar to those seen in infants dying with systemic herpes simplex or salivary gland virus infections. This is an excellent article on the suggested relationship between neonatal infections and viral, especially Coxsackie group B, etiologies.

Fatalities Occur

Kibrick and Benirschke, at approximately the same time, were reporting two additional cases of neonatal infections with group B Coxsackie (type 4) virus, both ending fatally.[9] The first case involved a ten day old infant who died within a four and one-half hour period after admission to the hospital with a picture of sepsis associated with congestive heart failure. Coxsackie group B type 4 virus was present in the myocardium in high titer and also was isolated from the feces of two siblings as well. Serological tests on both parents' serum was highly suggestive of a recent Coxsackie group B type 4 infection. At postmortem examination, there were microscopic changes in the myocardium, liver, pancreas, brain and spinal cord. The second case involved a female infant who died at thirty-six hours of life; the viral agent was recovered from the myocardium, spinal cord, and liver, as well as from the feces of the mother. The authors strongly felt that this infection had occurred in utero. The postmortem examination revealed extensive gastrointestinal hemorrhage and massive pulmonary bleeding. There were small foci of myocardial inflammation and degeneration irregularly scattered throughout the heart. The liver showed extensive parenchymal destruction throughout. There were also histological changes in the pancreas and adrenals as well as evidence of early fat necrosis. Likewise, there were histological changes in the brain and spinal cord. It was the authors' feeling that central nervous system involvement in Coxsackie group B virus infections in the neonatal period is relatively common; however, the clinical manifestations of meningitis in the neonatal period are relatively non-specific and may consist of cyanosis, fever, vomiting, lethargy, irritability, jaundice or irregular respirations. Even though one or more of the above signs were present in almost all of their patients, meningoencephalitis was usually not suspected since the predominant clinical features were suggestive instead of cardiac or respiratory disease, especially as the illness in several instances was initiated by sudden circulatory collapse. The authors further pointed out that, up to the time of their article, there were no reports of fatal infection in older children or adults due to the group B Coxsackie viruses. In the older age groups, infection with these agents has been manifested instead by an aseptic meningitis, epidemic myalgia, or by non-specific febrile illnesses.

Noteworthy was Kibrick and Benirschke's unexpected finding of severe destruction of the anterior horn cells, indistinguishable from that of poliomyelitis, in the spinal cords of the first-passage suckling mice inoculated with the agents recovered from the patients in their study. They further noted that in several patients with the clinical diagnosis of paralytic poliomyelitis, attempts to recover poliovirus or to demonstrate antibody response to this agent have not been successful. From several such patients, however, a group B Coxsackie virus has instead been isolated.[10, 11] One child developed extensive paralysis of the right leg and was admitted with the clinical diagnosis of poliomyelitis, but no such virus could be recovered from the feces, which did, however, yield Coxsackie group B type 4 virus. Kibrick and Benirschke point out that this was the same agent that was responsible for the production of the lesions of the anterior horn cells in suckling mice in both of the cases reported by them; and it was their feeling that this was highly suggestive that certain strains of these Coxsackie agents may be capable of inducing poliomyelitis-like lesions, associated with muscle weakness, in man.[9]

Earlier, Kibrick and Benirschke had presented evidence for intrauterine infection with a Coxsackie group B (type 3) virus in an infant in whom meningoencephalitis

developed with resultant death seven days after delivery.[5] The mother was well until the 38th week of her pregnancy when she developed symptoms of an upper respiratory illness with coryza, sneezing and malaise. Two days later she bled vaginally and the diagnosis of placenta previa was made and a resultant emergency Caesarean section was performed. Several hours post birth the infant developed a croupy cough and inspiratory crow. Lumbar puncture was performed on the fifth day of life and revealed clear, xanthochromic fluid under normal pressure with a two-plus Pandy and one hundred thirty-two white blood cells per cubic millimeter, ninety-five per cent of which were mononuclear in type. A repeat lumbar puncture the next day revealed three hundred and twenty-seven while blood cells per cubic millimeter, again ninety-five per cent of which were mononuclear. The child was treated with antibiotics but suffered a progressive downhill course and died. The postmortem examination showed a diffuse myocarditis, encephalitis, and degenerative and inflammatory changes in the lateral aspects of the anterior horns of the spinal cord. Virus isolation of the Coxsackie group B type 3 was made from the thoracic cord sections at postmortem examination. They noted at that time that the clinical picture was characterized by a relatively sudden onset, with anorexia, evidence of circulatory and respiratory embarrassment, and a tachycardia with rapid progression to death or recovery. In the case described, neutralizing antibodies for the agent in the blood specimen taken from the mother were found.

Case Presentations

Case No. 1

Case No. 1 was the result of a normal, full term spontaneous delivery after two hours of labor, being born on September 2, 1958. The newborn physical examination and the three day physical examination by the house officers plus the physical examination by the private pediatrician revealed nothing abnormal. There was no history of the infant vomiting or having diarrhea during his hospital stay, and he was discharged on September 6, 1958 after an uneventful, afebrile four-day neonatal period. The baby weighed seven pounds, eight ounces at birth and was discharged with a weight of seven pounds, five ounces. The mother was gravida II, para II, Rh positive and had had an uneventful pregnancy except for German measles contracted during the sixth month of pregnancy.

Infection Symptoms Obscure

Four days after discharge, the patient was readmitted with a six hour history of fever of one hundred two and five-tenths degrees. The baby had fed well that day with no history of drowsiness, lethargy, irritability, vomiting, diarrhea or respiratory distress. Both the parents were said to be in good health at the time of birth and immediately following it, as was the other sibling at home. However, the parents did mention that there appeared to be a lot of diarrhea in the neighborhood. The baby was seen at home just prior to his admission and nothing was noted on physical examination except a questionably full fontanelle which was not tense or pulsating.

Physical examination on admission to the hospital revealed a well-developed, well-nourished white male in no acute distress. The pulse was one hundred and ten per minute and regular; respirations were twenty-four and regular; temperature one hundred two and two-tenths degrees. Examination of the head, ears, eyes, nose and throat was unremarkable except for the above mentioned full fontanelle and an inconstant nystagmus to the left, which had never been noted previously. There was no nuchal rigidity or retraction, and the neck was passively flexed without difficulty. The lung and heart findings were normal and the rest of the physical examination, including the neurological examination, was unremarkable.

Soon after admission, because of the full fontanelle and evidence of a nystagmus not previously known to be present, a lumbar puncture was performed which revealed an opening pressure of one hundred and ten

millimeters of cerebrospinal fluid. Approximately six to seven ccs. of cloudy cerebrospinal fluid was removed and sent for analysis which revealed: cells ,two thousand white blood cells per cubic millimeter, seventy per cent being mononuclear cells; Pandy, four plus; protein one hundred forty-six milligrams per cent; sugar fifty-two milligrams per cent; chloride, one hundred twenty-three meq/1. Three slides were prepared from the cerebrospinal fluid specimen and stained with Gram's stain and careful microscopic examination failed to reveal any organism. Admission laboratory work revealed a hemoglobin of fifteen and eight-tenths grams with a white blood count of fifteen thousand one hundred; the differential count revealed fifty per cent polys, eleven per cent bands, thirty-four per cent lymphocytes, three per cent monocytes and two per cent eosinophiles.

Because it was felt that this baby probably had a bacterial meningitis, most likely E. coli statistically, chloromycetin, sulfadiazine, and penicillin therapy was initiated pending the report on the cerebrospinal fluid cultures. The temperature remained at one hundred and two degrees for the first twelve hours and then fell, in a typical lytic curve, to normal where it remained throughout the baby's hospital stay. Since the cerebrospinal fluid culture was negative and the baby was doing well clinically, the penicillin was discontinued on September fifteenth and the sulfadiazine discontinued on September sixteenth. A second spinal tap was performed on September eighteenth, eight days after admission, and the specimen obtained was slightly cloudy with a two plus Pandy; there were three hundred twenty-nine white blood cells per cubic millimeter, ninety per cent of which were lymphocytes; many RBC were noted; the protein was one hundred milligrams per cent and the cerebrospinal fluid sugar was thirty-eight milligram per cent. Chloromycetin was discontinued on September nineteenth and the baby had an uneventful recovery until discharge on September twenty-first. There was no clinical evidence of cardiac involvement; unfortunately, no electrocardiogram was taken. The nystagmus disappeared after the first forty-eight hours.

Laboratory Data

Culture of the umbilical cord grew out E. coli and alpha streptococcus. The two cerebrospinal fluid cultures submitted revealed no growth after an appropriate time interval. The throat culture grew out hemolytic Staphylococcus albus, coagulase negative, and alpha streptococcus. Blood culture taken on admission revealed no growth.

The first two blood samples sent for virus studies were negative for evidence of lymphocytic choriomeningitis, mumps, and polio virus 1, 2 and 3 antibodies. The first stool specimen sent failed to show any virus present; however, from the second stool specimen Coxsackie group B type 5 was isolated as was also done from the throat swab taken for viral studies.

The parents were contacted approximately one month after this child's illness and an extensive effort was made to elicit some indication of an infection in the family at the time that this child became ill. However, aside from the history of diarrhea in the neighborhood, no history suggestive of any type of infection could be elicited.

Case No.2

Case No. 2 is a seven year old white boy who was admitted on August seventeenth, 1958, with a twelve hour history of vomiting, stiff neck and fever. The patient, a physician's son, and the rest of the family had just returned from a vacation in New Hampshire where three of the five children, including the patient, were said to have contracted viral upper respiratory infections. The patient had had a rather severe cough and had been treated with Gantrisin. That illness had lasted approximately seven days, ending about five days prior to admission. Some time during the night prior to admission, the patient vomited but did not call out to his parents; however, that morning he awoke with a stiff neck and called for his parents. At this time the father also noted the evidence of a stiff neck. Later that day, the patient developed a fever of one hundred two degrees and

was admitted to the hospital. Physical examination revealed a pulse of one hundred ten per minute which was regular; a temperature of one hundred two degrees; and a respiratory rate of twenty-two per minute which was regular. He was a well developed, well nourished white made of seven, lying quietly in bed in no acute distress but appearing ill. He was alert and oriented as to time, person and place. There was no sign of dehydration, shortness of breath, cyanosis or jaundice. Positive physical findings were limited to: 1) slightly injected throat; 2) slight muscular soreness in the neighborhood of the neck but the neck could be flexed fairly well and there was no evidence of opisthotonus; 3) negative Kernig's and Brudzinski's signs; and 4) physiological deep tendon reflexes.

Laboratory Data

There was no evidence of any abnormal neurological findings. Laboratory data on admission revealed a hemoglobin of fifteen and three-tenths grams with hematocrit of thirty-nine. White blood count was twelve thousand nine hundred and fifty with sixty-six polys, five bands, twenty-eight lymphocytes and two monocytes. A repeat hemogram on the following day revealed a hemoglobin of thirteen and two-tenth grams with an hematocrit of thirty-eight and a white blood count of eight thousand eight hundred, the differential showing sixty-two per cent polys, two per cent bands, twenty-four per cent lymphocytes, four per cent atypical lymphocytes and six per cent monocytes. The admission urinalysis was unremarkable. A lumbar puncture was performed soon after admission and the opening pressure was greater than two hundred and seventy-five millimeters of cerebrospinal fluid (the patient vomited just after this reading), and about ten cc. of clear, colorless fluid was removed without incident. The closing pressure was one hundred to one hundred fifty millimeters of cerebrospinal fluid. Analysis of the cerebrospinal fluid revealed: 1) one hundred twenty-nine white blood cells per cubic millimeter, ninety per cent being mononuclear cells; 2) negative Pandy; 3) ninety-two milligrams per cent protein; 4) fifty-five milligrams per cent sugar; and 5) one hundred nine mEq/1 of chloride. First and intermediate strength PPD's were applied and read as negative subsequently.

Progress in the hospital: The patient was seen on August twentieth by a neurologist because of pain radiating down the left leg. Physical examination at that time revealed slight nuchal stiffness and evidence of stiffness down the back of the left leg. There were no other physical findings and the neurological examintion was completely negative. He was again seen by the neurologist the following day who felt the neck was slightly stiffer and noted pain to be present down both legs on straight leg raising tests. The temperature came down to normal during the first forty-eight hours of hospitalization and the patient was discharged on August 24, 1958, after conservative therapy was administered.

Culture of the throat revealed normal flora. The first two blood specimens were negative for evidence of lymphocytic choriomeningitis, mumps, and polio viruses 1, 2 and 3 antibodies. However, Coxsackie B type 5 was isolated in tissue culture from the throat washings, cerebrospinal fluid, and three stool specimens submitted.

Case No. 3

Case No. 3 is a three year old white boy who was admitted on October 1, 1958 with an eighteen hour history of muscle pain, elevated temperature to one hundred four degrees, and chills. There was no history of lethargy, nausea, vomiting or diarrhea. Pain was present in the arms and legs, crampy in nature and relieved somewhat by massaging and heat. One sibling had had an elevated temperature for a twenty-four hour period four days prior to admission of the patient and this sibling had vomited one time. There was no history of joint or muscle pain in the affected sibling. The father had had an upper respiratory infection and sore throat one week prior to the patient's admission.

The patient was the result of a normal full term spontaneous delivery after a five

hour labor with a birth weight of six pounds, twelve ounces and a resultant normal development. An episode of chicken-pox was the only childhood disease encountered. The patient had been admitted two years prior to this admission for evidence of portal obstruction with esophageal hemorrhage. There was a history of diabetes on both the maternal and paternal sides of the family.

Laboratory Data

Physical examination on admission revealed a well developed, slightly malnourished white boy of three years complaining of generalized severe muscle cramps. Positive physical findings revealed: 1) the spleen was down to the level of the umbilicus; 2) the liver was not felt: 3) the muscles of the extremities were intermittently spastic and firm associated with severe pain when touched. The neurological examination was entirely within normal limits. Laboratory data on admission revealed a hemoglobin of eleven and six-tenths grams with hematocrit of thirty-four. The white blood count was twelve thousand one hundred with fifty-nine polys, fourteen bands, twenty-three lymphocytes and four monocytes with evidence of slight toxic degeneration on the smear. The platelet count was ninety-seven thousand. Admission urinalysis was essentially unremarkable. The calcium was ten and four-tenths milligrams per cent and the phosphorus was two and nine-tenths milligrams per cent. The alkaline phosphatase was ten units.

Progress in the hospital: The patient was afebrile throughout his entire hospital stay and the muscular cramps were gone within a period of twenty-four hours. He was treated with aspirin and hot compresses, being discharged on October 3, 1958, with a final diagnosis of viral myositis. Throat culture grew out alpha streptococcus. Coxsackie group B type 5 virus was isolated from the throat washings and stool cultures.

REVIEW OF COXSACKIE GROUP B TYPE 5 INFECTIONS

Coxsackie group B, type 5, was first isolated by Steigman in 1952.[12] Since that time numerous forms of infection have been attributed to this one particular type of virus. Syverton and his associates, in an attempt to elicit the etiologic agent(s) of the many cases seen of "non-typical poliomyelitis" accordingly undertook in 1956 a program to establish the viral etiology of each aseptic illness involving the central nervous system not proved to be poliomyelitis.[13] The occurrence of an epidemic form of aseptic meningitis in Minnesota in the summer and autumn of 1956 afforded this opportunity. In this outbreak of aseptic meningitis, Coxsackie virus strains were isolated from sixty-two patients ill between July and December, 1956. The virus was isolated in submitted stool and/or throat washing specimens anywhere from the first to the twelfth or thirteenth day of onset of the illness. None was isolated from the cerebrospinal fluid of patients in their series.

False Reports In 1956

During 1956, Minnesota physicians reported one hundred seventy-nine illnesses categorized as "epidemic poliomyelitis." Sixty-six patients had one or more limbs paralyzed: forty-two patients with paralytic and five with non-paralytic disease yielded viruses classified as thirty-nine strains of type 1 and eight strains of type 3 polioviruses. The one hundred thirteen patients with no indication of paralysis had various diagnosis made. They yielded sixty-two viruses other than poliovirus and sixty-one of these sixty-two viruses were identified as Coxsackie virus, immunotype B 5. Evidence against concurrent polio virus infection was given by 1) failure to isolate polio virus from the sixty-one patients with aseptic meningtitis who yielded Coxsackie group B, type 5 virus; 2) insignificant changes in titer of antibody in forty-two paired samples of patients' serum to types 1 through 3 polio virus; and 3) occurrence of aseptic meningitis without relation to history of vaccination with formalin inactivated trivalent polio vaccine.

On clinical grounds alone, the syndrome exhibited by the sixty-one patients infect-

ed with Coxsackie group B, type 5 virus could not be distinguished from non-paralytic disease caused by infection with polio virus. In this quite large series, the age range was from six months to forty-five years, the largest number of cases, however, occurring in the age group of five to nine years. Symptoms included sudden onset of fever with severe headache, stiff neck or back, leg pains or gastrointestinal symptoms. The cerebrospinal fluid showed a pleocytosis, predominantly lymphocytes. Weakness or paralysis of the limbs was not a feature of their cases of aseptic meningitis.

Coincidentally, at the same time, Rubin and his group were studying an epidemic of aseptic meningitis which occurred during the summer of 1956 in Iowa.[14] A total of sixty-three hospitalized and fifty-two non-hospitalized patients were studied. Again, specimens of serum, stool, throat washings and cerebrospinal fluid (if obtained) were submitted for the etiological diagnosis.

Broad Clinical Spectrum

The outstanding characteristic of this illness was the broad clinical spectrum which presented itself, ranging from very minor symptoms to the syndrome of aseptic meningitis requiring hospitalization. The latter patients appeared acutely ill and usually presented with the chief complaints of severe headache and stiff neck. Myalgia was also noted in over one-third of the hospitalized patients.

Coxsackie virus group B, type 5 was isolated from the stools, throat washings and cerebrospinal fluid specimens, the greatest number of isolations being obtained from stool specimens. It should be noted that only two of the nineteen cerebrospinal fluid specimens submitted were able to show isolation of this one particular virus. Isolation of the virus from the stool specimens occurred anywhere from the first to the thirty-sixth day of illness.

Fluid Analysis

Cerebrospinal fluid analysis in those patients from which it was obtained revealed a count anywhere from zero to two thousand four hundred white blood cells per cubic millimeter with an average of five hundred seventy cells and a median of four hundred twenty-four cells per cubic millimeter. The differential count on the cells in the cerebrospinal fluids usually showed a lymphocytic response although polymorphonucleated cells were seen early in the illness. The total protein of the cerebrospinal fluid varied from fifteen to ninety milligrams per cent with an average of forty-one milligrams per cent. Admission white blood counts in their series ranged from four thousand five hundred to twenty thousand; sixty-seven per cent of the white blood counts were less than ten thousand. The great majority of the differential counts were within normal limits. Interestingly enough, the authors point out that the absence of nuchal rigidity does not rule out the aseptic meningitis syndrome, the highest count (two thousand four hundred white blood cells per cubic millimeter) in the cerebrospinal fluid occurred in a patient with only questionable meningeal irritation. One-third of all of their cases occurred in the age group of five to nine years and two-thirds of all cases occurred in people less than twenty years of age. Weinstein, however, does recount the case of acute benign pericarditis in a twenty-five year old man associated with a Coxsackie virus group B type 5 infection.[15]

Person To Person

Rubin and his group felt that the spread of the infection was by person to person contact, either by means of the gastrointestinal tract or from the oropharynx. The incubation period is felt to be three to five days.

Discussion

It is felt that the three cases presented in this rather short series are representative of the spectrum of disease which a Coxsackie group B, type 5 virus may cause. Certainly the first case presented falls within the accepted criteria for the diagnosis of aseptic meningitis. Since there was no evidence of a bacterial infection, it is felt

that the etiological agent was definitely the Coxsackie group B type 5 virus. On the basis of what is felt to be a three to five day incubation period for this particular agent, the infant must have contracted his illness either on the day of discharge from the hospital or during the following twenty-four hours at home. We certainly do not postulate that this was an intrauterine infection. Unfortunately, no blood specimens or stool cultures were obtained from either parent or sibling, and certainly we have no reason to implicate them, especially in view of their repeated denials of any symptoms suggestive of an illness. It is felt that this represents the first case of aseptic meningitis due to Coxsackie group B, type 5 in a child as young as this one was. In retrospect, in view of the rather poor prognosis that one obtains in reviewing the literature, we certainly feel quite fortunate that this child recovered in such an easy fashion. Whether other organs were involved in this infection, notably the heart, we have no way of proving. It is unfortunate that an electrocardiographic tracing was not taken during the first twenty-four hours of admission. We feel quite certain that the antibiotic therapy employed in this particular case had nothing to do with the infant's recovery.

Can Viruses Cause Paralysis?

The second case is of particular interest in that without appropriate viral studies this child most likely would have had the final diagnosis of non-paralytic poliomyelitis. Certainly the clinical course and the laboratory findings would be compatible with this diagnosis. This case is of further interest in that it affords a stepping stone to the discussion of whether viruses other than the polio viruses can cause paralysis. During this child's first three to four days of hospitalization, the possibility of this being a paralytic poliomyelitis certainly was entertained. Several observers who examined the child felt that there was evidence of muscular weakness developing in the left leg. At any rate this did not progress to any sufficient degree, and at the time of discharge the child had no evidence of any muscular weakness.

Similarities Of Clinical Poliomyelitis To Coxsackie Viruses

Hammon and his group feel that it has been shown that certain enteroviruses, such as Coxsackie A$_7$, ECHO-2, ECHO-6, ECHO-9, and some Coxsackie group B, may cause paralytic illnesses resembling poliomyelitis clinically.[16] Their report further showed that other members of the Coxsackie and ECHO groups may or actually do cause mild paralysis. Three cases of clinical paralytic poliomyelitis-like disease without evidence of concurrent polio infection were presented. From these three particular cases a Coxsackie virus was isolated one was due to Coxsackie B-4; the second was due to Coxsackie B-3, and the third was felt to be due to Coxsackie A-9. They further presented three paralytic cases probably without poliovirus infection in which ECHO-16 and ECHO-4 viruses were isolated. They emphasized that these six illnesses had been diagnosed as clinical paralytic poliomyelitis by a team of experienced poliomyelitis clinicians. It is now felt that these illnesses represent "paralytic poliomyelitis-like" cases since, essentially, there was no laboratory evidence of a poliomyelitis infection.

Likewise, Blattner reviewed the problem of poliomyelitis-like illnesses and feels that there is incriminating evidence to suggest that many of these diseases are caused by both group A and group B Coxsackie viruses.[2]

Habel and Loomis discussed the relationship of Coxsackie group A, type 7 virus and the Russian poliovirus type 4.[17] The latter virus had been isolated from fecal specimens obtained from children during an acute phase of a clinical illness which seemed to have the classical characteristics of paralytic poliomyelitis. The authors later proved that this virus was identical with stains of Coxsackie group A, type 7 virus isolated from children with aseptic meningitis. According to the authors, these Coxsackie A-7 strains, like the Russian polio

virus type 4, "are capable of producing in the central nervous system of some monkeys, lesions which are indistinguishable from those caused by polio viruses." They concluded that "certainly our present knowledge. . .should emphasize the necessity of search for these other viruses in paralytic cases where the specific etiology of poliovirus cannot be established." Likewise, one must not consider the polio vaccine to be a "failure" till proven by appropriate isolation and serological tests that the particular paralytic infection is due to a poliovirus and not one of the other enteroviruses. The present author feels that it is extremely important that disease suggestive of poliomyelitis be proven to be so by appropriate viral studies. This type of approach to the problem certainly is necessary in evaluating the presence of an "epidemic" or the value of the present poliomyelitis vaccine.

The third case presented certainly does not represent a serious illness when compared to the other two cases. One must go even further in saying that this illness was *associated* with a Coxsackie group B, type 5 virus; certainly we cannot prove that the signs and symptoms were definitely related to this particular etiological agent. It is well known that a large percentage of children during the summer and autumn months excrete enteroviruses without being clinically ill. Therefore, one cannot rationally exclude the possibility that this child's problem was on the basis of an etiological agent other than the Coxsackie group B, type 5 virus. However, circumstantially, the latter virus would seem to be the most likely etiological agent.

Summary

A review of part of the literature on Coxsackie Group B infections in children is presented, with special reference to the various clinical entities caused by Coxsackie Group B, type 5 virus.

Differential Diagnosis

Three cases are also presented in an attempt to show the spectrum of disease which may be caused by the Coxsackie group B, type 5 virus. The first case presented is that of aseptic meningitis in a nine day old infant. It is felt that this case represents the first reported of an infection of this type with Coxsackie group B, type 5 virus in an infant this young. The second case is that of a poliomyelitis-like illness and it is suggested that all illnesses of this type be studied fully from the viral diagnostic aspect. The final case presented is a relatively benign one with signs and symptoms suggestive of a myalgia.

References

1. Dalldorf, G. and Sickles, G. M.: An Unidentified Filtrable Agent Isolated From the Feces of Children With Paralysis, Science 108: 61, 1948.
2. Blattner, R. J.: Poliomyelitis—Like Illnesses, J. Ped. 52: 111, 1958.
3. Dalldorf, G.: The Coxsackie Viruses, Ann. Rev. Microbiol. 9: 277, 1955.
4. Parrott, R. H.: Newly Isolated Viruses In Respiratory Disease, Ped. 20: 1066, 1957.
5. Kibrick, S. and Benirschke, K.: Acute Aseptic Myocarditis and Meningoencephalitis in the Newborn Child Infected With Coxsackie Virus Group B, Type 3, Nej Med. 255: 833, 1956.
6. McLeod, D. L., Beale, A. J., McNaughton, G. A., and Rhoades, A. J.: Clinical Features of Aseptic Meningitis Caused By Coxsackie B Virus, Lancet 2: 701, 1956.
7. Javett, S. N., Heymann, S., Mundel, B., Pepler, W. J., Lurie, H. I., Gear, J., Measroch, V., and Kirsch, Z.: Myocarditis In the Newborn Infant, J. Ped. 48: 1, 1956.
8. Hosier, D. M. and Newton, W. A.: Serious Coxsackie Infection In Infants and Children, A.M.A.J. Dis. Child. 96: 251, 1958.
9. Kibrick, S. and Benirschke, K.: Severe Generalized Disease (Encephalohepatomyocarditis) Occurring In the Newborn Period and Due To Infection With Coxsackie Virus, Group B, Ped. 22: 857, 1958.
10. Hammon, W. McD., Yohn, D. S., Ludwig, E. H., and Sather, G. E.: Echo Coxsackie and Unidentified Viruses Associated With Polio-like Disease, Bact. Proc., 1957, p. 73.
11. Kumm, H. W.: Relationship of Echo and Coxsackie Viruses To Paralytic and Non-paralytic Polio, J-Lancet 77: 469, 1957.
12. Stefgman, A. J., Discussion, Part I. Coxsackie Viruses, Ann. N. Y. Acad. Sc. 67: 249, 1957.
13. Syverton, J. T., McLean, D. M., Martins da Silva, M., Doany, H. B., Cooney, M., Kleinman, H., and Bauer, H.: Outbreak of Aseptic Meningitis Caused By Coxsackie B 5 Virus, J.A.M.A. 164: 2015, 1957.
14. Rubin, H., Lehan, P. H., Doto, I. L., Chin, T. D. Y., Heeren, R. H., Johnson, O., Wenner, H. A., and Furcolow, M. L.: Epidemic Infection With Coxsackie Virus Group B, Type 5, N. E. J. Med. 258: 255, 1958.
15. Weinstein, S. B.: Acute Benign Pericarditis Associated With Coxsackie Virus Group B, Type 5, N. E. J. Med. 257: 265, 1957.
16. Hammon, W. M., Yohn, D. S., Ludwig, E. H., Pavia, R. A., Sather, G. E., and McCloskey, L. W.: A Study Of Certain Non-poliomyelitis and Poliomyelitis Enterovirus Infections, J.A.M.A. 167: 727, 1958.
17. Habel, K. and Loomis, L. N.: Coxsackie A_7 Virus and The Russian "Poliovirus Type 4," Proc. Soc. Experim. Biol. and Med. 95: 597, 1957.

Addendum

The author wishes to express his sincere appreciation to Dr. Klaus Hummeler of the Virus Diagnostic Laboratory of the University of Pennsylvania for performing the necessary viral diagnostic tests in order to establish the etiological agents in these particular cases.

The author also wishes to thank Dr. Henry Stroud and Dr. John Maroney for permission to use the cases on their private services in the presentation of the three cases described.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS OF ANEMIA*

● The final section of Part II concludes the author's comprehensive outline on a subject which must always be considered as a "danger signal symptom" in a patient.

ANDREY GEORGIEFF**

The following anemias are due to intracorpuscular causes:

1) *Hereditary spherocytosis* (also called congenital hemolytic jaundice etc.). This is a familial and hereditary disorder characterized by spherocytosis, increased osmotic fragility of the red blood cells, splenomegaly, and a variable degree of hemolytic anemia.

Jaundice and splenomegaly are the most common manifestations and may pass unnoticed for many years. Symptoms of anemia are usually absent or mild. At any time from birth to late adult life, attention may be drawn to the disorder by the crisis of deglobulization, which is characterized by fever, lassitude, palpitation, and shortness of breath or even violent abdominal pain, vomiting, and anorexia.

The life span of red blood cells is very brief.

The anemia is usually moderate in degree but may be very mild or severe. It is normocytic or simple microcytic in type but, when severe and associated with market reticulocytosis, it can be marcrocytic. There is little poikilocytosis, but small bright, deeply staining red blood cells (spherocytes) are often seen among the cells of normal size. Reticulocytes are characteristically increased in number. Polychromatophilia and normoblasts may be seen in the blood smear. The leukocytes are usually normal in number or slightly increased. The platelet count is generally normal. Increased osmotic fragility of the red blood cells is characteristic. There is bilirubinemia of the "indirect" type and increased quantities of urobilinogen in the urine and stools, without bile in the urine (acholuric). The Coombs' test is negative.

Differential diagnosis: It is especially important to distinguish cases of congenital non-spherocytic anemia because they have not been benefited by splenectomy.

2) *Hereditary non-spherocytic hemolytic anemia:* Although such cases resemble hereditary spherocytosis in their mode of inheritance, they differ in that the anemia is generally macrocytic; there is often a moderate degree of ovalocytosis, and sometimes there is conspicuous punctate baso-

*Third section of Part II. The first part of the article "Anemia" appeared in the November, 1958 issue of the JOURNAL.

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philia. Spherocytes are not found, and osmotic fragility is normal.

3) *Thalassemia* (*Mediterranean anemia*). This is a hypochromic microcytic anemia which is characterized by the presence of unusually thin red blood cells, miscrocytosis, various degrees of anemia, and, when the anemia is severe, numerous nucleated red blood cells. In Thailand, it is the most common hemolytic anemia.

The full-blown disorder (Thalassemia major, Cooley's anemia) develops insidiously within the first year or two of life, and is marked by pallor and great enlargement of the spleen and even the liver. Roentgenograms reveal great thickening of the diploe of the skull with perpendicular striation, increase in the medullary portion of the long bones with thinning of the cortex, and other changes attributable to the extreme hyperplosia of the bone marrow. The anemia is severe, hypochromic and microcytic in type, and the red blood cells contain so little hemoglobin and are so thin that they produce forms which have the appearance of targets. Fragility tests in hypotonic saline solutions reveal that the red blood cells are unusually resistant to hemolysis by this means. Nucleated red blood cells and microblasts are seen, also there is anisocytoses, poikilocytosis, target cells, polychromatophilia, basophilic stippling, Howell-Jolly bodies, moderate reticulocytosis, and leukocytosis with shift to the left. There is usually slight or moderate bilirubinemia, with a corresponding increase in the urobilinogen content of the urine and stools.

Thalassemia minor, on the other hand may pass entirely unnoticed, since painstaking examination may be necessary to reveal any abnormality. Slight anemia, splenic enlargement, microcytosis and hypochromia, target cells, poikilocytosis out of proportion to the existent anemia, decreased hypotonic saline fragility, basophilic stippling of the red blood cells, and bilirubinemia are some of the signs which, singly or in various combinations, mark this disorder. Roentgenographic changes in the bones similar to, though less pronounced than those found in the severe form, may be observed.

The degree of penetrance of the Thalassemia gene seems to vary greatly. There is a wide range in the manifestations of the heterozygous condition. The term *Thalassemia minima* refers to those instances in which the manifestations are very slight. In some persons the number of red blood cells is actually increased above normal although, since the red blood cells are usually microcytic and hypochromic, the hemoglobin and hematocrit are usually slightly below the average normal values.

Differential Diagnosis in Thalassemia: Plumbism, congenital hemolytic jaundice, and sickle-cell anemia are among the disorders which must be distinguished on the basis of the characteristics already described.

4) *Sickel-cell anemia* is a hereditary anemia characterized by the presence of red blood cells which, under appropriate conditions, assume sickle-shaped or oat-shaped forms. Inheritance of the abnormality from any one parent, the heterozygous state, is represented by the sickle-cell trait, in which sickling of the red blood cells can be demonstrated but is not accompanied by symptoms of anemia. Sickle-cell anemia is the homozygous state in which one abnormal gene has been inherited from each parent. Sickle-cell anemia possesses all the characteristics of a chromic hemolytic anemia with certain special features as well.

The red blood cells of patients with sickle-cell disease contain sickle-cell hemoglobin (S Hemoglobin).

The ratio of S hemoglobin to normal hemoglobin (A hemoglobin) in the blood of individuals with sickle-cell trait is from 22 to 45%, while the amount in the blood of this with sickle-cell anemia is 76 to 100%.

Symptoms: Jaundice and a chromic anemia with few or no complaints are interrupted by periods of increased weakness,

episodes of aching pain in the joints or elsewhere in the extremities, or sudden attacks of severe abdominal pain. Roentgenograms may reveal radial striation in the skull, osteoporosis in the vertebral bodies, or other changes in the long bones.

The anemia is usually surprisingly severe, erythrocyte counts below 2.5 million being common. The anemia may be normocytic or macrocytic. Oval, cigar-shaped, or other bizarre forms of red blood cells may be seen in the stained smear. The sickling is brought out clearly in wet films of blood which have been fixed under a cover glass and sealed with paraffin. In cases with sickle-cell anemia the typical sickled and oat-shaped forms with elongated, pointed filaments appear within a few hours. When only the sickle-cell trait exists, 24 hours is often required to produce this change and only a proportion rather than practically all of the cells are affected. By the use of reducing agents such as Na bisulfate, sickling can be hastened and the characteristic forms appear promptly.

In sickle-cell anemia there is reticulocytosis, polychromatophilia, normoblasts, leukocytosis with "shift to the left", increase platelets, hyperbilirubinemia and increased urobilinogen in the urine and stools. Osmotic fragility is decreased, not increased. The bone marrow shows striking normoblastic hyperplasia.

In distinguishing persons with the sickle-cell trait that have some disorder accompanied by anemia from those who have sickle-cell anemia, it must be kept in mind that the former may develop any type of anemia, while in the latter the anemia is always hemolytic in type.

5) *Microdrepanocytic disease* is the name given to the combination of sickle-cell and Thalassemia genes which results in a chromic hemolytic anemia with some of the characteristics of both sickle-cell disease and Thalassemia. The Thalassemia trait has also been observed in association with hemoglobin C, hemoglobin E, and other hemoglobins. Some of the clinical and hematologic manifestations of these combinations are outlined in the table below.

6) *Other (besides sickle-cell anemia and Microdrepanocytic disease) abnormal hemoglobin syndromes (hemoglobinopathies).* The hemoglobin of normal red blood cells is called hemoglobin A. In sickle-cell anemia and sickle-cell trait, the red blood cells contain hemoglobin A and hemoglobin S.

a) Hemoglobin C is the name given to a third type of adult hemoglobin. The incidence in the United States of the gene responsible for hemoglobin C is about 2% in the Negro population, as compared with about 9% for S hemoglobin. Carriers of hemoglobin C are asymptomatic, but target red cells are found in their blood. The hemozygous state is characterized by the presence of a normocytic hemolytic anemia of mild degree or no anemia whatsoever. More than two dozen cases of homogygous hemoglobin C disease have been reported, all in Negroes with but two exceptions.

b) A number of instances have been discovered in which both S and C hemoglobin were demonstrated. The combination of hemoglobin S with C hemoglobin is accompanied by sickling of red blood cells as well as by hemolytic syndrome similar to sickle-cell anemia but differing in that the hemolytic anemia is milder and target cells are more plentiful in the blood.

c) Hemoglobin D is very rare.

d) Hemoglobin E has been found in 13% of the population of Thailand and has been encountered frequently in association with the gene for Thalassemia.

e) Hemoglobin G has been found in Negroes in West Africa.

f) Hemoglobin H has been found very rarely in China, Greece, and Thailand.

g) Hemoglobin I has been found in a Negro family.

h) Hemoglobin J and K have been reported.

In general the trait conditions of the hereditary hemoglobinopathies (heterozygosity) are not associated with a hemolytic anemia or morphologic abnormalities in the blood. The only exception of this rule is the presence of target cells in hemoglobin C trait. As a general rule the homozygous state usually results in a definite hemolytic anemia of varitable severity. An exception to this rule is Hemoglobin C. disease. As another general rule, heterozygosity for two abnormal Hb. genes usually results in hemolytic anemia. However, the gene for hemoglobin G is not associated with detectable-physiologic disturbance. Another rule is that if hemoglobin S is present, either alone or in any combination, the sickle-cell test will be positive.

Hemoblobin S and hemoglobin C, with rare exceptions, are limited to Negroes.

7) *Paroxysmal nocturnal hemoglobinuria (Marchiafava-Micheli syndrome)*. This is a rare disorder, characterized by signs of hemolytic anemia and is marked by attacks of hemoglobinuria which occur chiefly at night. The fault resides in the red blood cells, which are usually susceptible to acid hemolysis. There is a simple test for demonstarting this. The destruction of the cells is promoted by the accumulation of CO_2 during sleep, an optimum acid pH being required for hemolysis to take place. The name of the test is "Test for Acid Hemolysis".

The defect in the *extra corpuscular hemolytic anemia* lies in the environment of the cells and not within the r.b. cells themselves. Thus, when erythrocytes from a patient with an extracellular type of hemslytic anemia are removed from their unfaxorable environment and are transferred (Test for survival time of r.b. cells) into a normal recipient, they survive for a normal period of time. The extracorpuscular hemolytic anemias are acquired diseases and are not hereditary.

Most extracorpuscular hemopytic anemias are associated with detectable autoantibodies, some with isoantibodies, and in some no antibodies can be demonstrated. In every case of hemolytic anemia look for extracorpuscular causes. Those causes are enumerated in the table of Etiologic classification of anemia. A few words about Paroxysmal cold hemoglobinuria:

Paroxysmal cold hemoglobinuria is an uncommon disorder characterized by the sudden passage of hemoglobin in the urine following local or general exposure to cold. The hemoglobinuria is due to the sudden intravascular hemolysis of blood as the result of the action of an autohemolysin contained in the patient's blood. Appropriated tests have been devised to demonstrate such a cold hemolysin. At the time of hemolytic attacks produced by chilling, strongly positive direct antiglobulin (Coombs') reactions have been observed, but they become negative after the attacks. The typical condition is manifestation of syphilis. A number of cases have been described, however, in which indications of syphilis were lacking.

III. Anemias Due to Decreased Rate of Red Blood Cells Formation

A. *Anemias due to inhibition (depression) of the rate of red blood formation*

1) Chronic infections are associated with profound disturbance in iron metabolism. This is manifested by a low plasma iron, reduced iron-binding capacity, and decreased incorporation of iron into hemoglobin. The defect cannot be altered by iron administration, even if iron is given parenterally in large quantities. The Anemias associated with infections are far more frequent than hemolytic anemia. Such anemia is usually only moderate in degree: hemoglobin values of 13 to 10 gm./100 ml. of blood are seen more frequently than lower values. The anemia is usually normocytic, and in the smear the red blood cells generally show little abnormality in size or shape, a monotonous picture unaccompanied by polychromatophilia, basophilic stippling, or nucleated red blood cells.

2) The anemias associated with chromic infection or with chromic renal, like aplastic anemia due to the action of a poison, is

differentiated from the anemias due to nutritional deficiency and the anemias due to exaggerated blood destruction by the lack of evidence of hematopoietic activity. Thus the anemia is usually normocytic, and is accompanied by relatively little poikilocytosis or anisocytosis; reticulosytes are normal in number and nucleated red blood cells are not found in the blood smear; the leukocytes are not altered in number from the normal except so far as they may represent a reaction to the underlying disorder.

The bone marrow in anemias due to infections show nothing characteristic. The nucleated red blood cells are of the normoblastic type. The marrow may appear hyperplastic, normal, or hypoplastic.

2. Chronic disease causes morphologic changes in the blood smear and bone marrow similar to these in chronic infection (see above).

3. Chemical and physical agents can depress the bone marrow.

4. Renal insufficiency (uremia) can cause anemia. Unlike the anemia associated with infection, anemia due to renal insufficiency does not have hypoferremia as a constant feature. Like the anemia of infection, however, the anemia of renal insufficiency is closely tied with the underlying disease and is uninfluenced by measures other than those which affect renal function. Corresponding rather closely to the gravity of the renal disorder, as manifested by the degree of retention of nitrogenous and other waste products, hemoglobin values as low as 5 gm/100 ml. are found; and the blood smear may reveal normoblasts, stippling and moderate anisocytosis and poikilocytosis. The anemia may be somewhat microcytic or hypochromic, and occasionally is macrocytic. The bone marrow is as in anemia due to chronic infections.

B. *Mechanical interference with blood formation in the bone marrow* (*Mechanical displacement of the bone marrow. Myelophthisic anemia*)

Leukemia, Hodgkin's disease, myelofibrosis, malignancy with metastasis to the bone marrow, multiple myeloma, and marble bone disease may cause anemia. The morphologic changes in the blood are as in anemia caused by chronic infection.

Malignant disease is not necessarily accompanied by anemia. Anemia accompanies malignancy in the G.I. tract more often than elswhere. In such cases nutritional deficiency may play an important role in the pathogenesis of the anemia, and in many cases, blood loss is also a contributory factor. Malignent disease of the kidney, breast, prostate, thyroid, and lungs, in particular, may metastasize to the bones, and in such an event "*myleophthisic*" *anemia* may develop. The picture then may be that of a pancytopenia, or a leukemoid picture may result. The latter is marked by leukocytosis together with a moderate "shift to the left" in the leukocytic formula, and normocytic anemia.

C. *Decreased formation of red blood cells due to deficiency of substances necessary for their production*

Macrocytic anemias are characterized by an increase in the volume (MCV) and weight of hemoglobin (MCH) in the red blood cells. The concentration of the hemoglobin in the red blood cells (MCHC) remains normal. The macrocytic anemias, in general, are of two types:

a) The megaloblastic macrocytic anemias are characterized by the presence of megaloblasts in the bone marrow. In these anemias, of which P.A. is the most common example, the administration of liver extract or vitamin B_{12} relieves the anemia, but in certain macrocytic megaloblastic anemias it is folic acid rather than vitamin B_{12} that relieves the anemia. In practice the most common cause of macrocytic anemia is laboratory error, and this is most often due to errors in red blood cell counting. Vitamin B_{12} and folic acid are valueless in anemias other than those in which the bone marrow is megaloblastic.

b) To be distinguished from the megaloblastic macrocytic anemias are the nonmegaloblastic macrocytic anemias. These

anemias are usually secondary to other disease and the bone marrow is non-megaloblastic.

These anemias are seen sometimes with hypothyroidism (Myxedema), liver disease, leukemia, lymphoma and some cases of aplastic anemia. Non-megaloblastic macrocytic anemias are also sometimes seen with a number of conditions which ordinarily produce normocytic anemia: acute post-hemorrhagic anemia, hemolytic anemia, and some other normocytic anemias. When there is intense activity of the bone marrow, the macrocytic here depends on the fact that a relatively large number of immature red blood cells (there is reticulocytosis etc.) appear in the circulation in response to hematopoietic stimulations and because in general, immature red blood cells are larger than mature, the anemia will be macrocytic instead of normocytic. Consequently, in conditions which ordinarily produce normocytic anemia, when there is an accompanying very intense activity of the bone marrow with liberation into the circulation of many immature cells, a temporarily macrocytic anemia develops.

The clinical differentiation between megalobastic macrocytic anemia and non-megaloblastic macrcocytic anemia is usually easy.

The clinical differentiation between megaloblastic macrocytic anemia and non-megaloblastic macrocytic anemia is usually

1) *Pernicious anemia*

The anemia is macrocytic with megaloblastic hyperplasia of the bone marrow.
Laboratory findings:

a) *Blood* Macrocytes are characteristically seen, but there is actually a great range in the size of the cells, and in addition, many bizarre-shaped red blood cells are found (poikilocytosis). The M.C.V. is greater than normal and ranges between 100 and 160 m. (The existence of a macrocytic anemia, as indicated by calculation of red blood cell size, should, furthermore, be confirmed by examination of the blood smear). The mean corpuscular hemoglobin contentration is normal. The red blood cells in P.A. and in other macrocytic anemias are not "hypochromic", but, being thicker as well as larger in diameter than normal red blood cells, they appear to be supersaturated with hemoglobin, as one looks at them through a microscope. Some degree of diffuse polychromatophilia as well as basophilic stippling is found, and occasional nucleated red blood cells may be encountered. Reticulocytics are usually within normal limits in untreated patients or, at most, do not run higher than three to four percent.

The leukocyte count is usually lower than normal and there is relative lymphocytosis. The polymorphonuclear neutrophilic leukocytes often show an unusual number of segments and may be exceptionally large. An occasional myelocyte is present in many cases. Sometimes some degree of eosinophilia is encountered. The platelets are generally reduced in number, sometimes to levels below one thousand per cubic millimeter.

The resistance of the red blood cells to hypotomic saline solutions is not significantly altered. In practically all cases the icterus index is elevated (usually between eight and fifteen; sometimes up to twenty-five), the plasma bilirubin is increased (the average bilirubin is 1 mg./100 ml. but sometimes is higher; the Van den Bergh reaction is "indirect").

b) *Other laboratory findings.* With extremely rare exceptions, there is, in P.A., persistent failure to secrete hemoglobin in the stomach even following the injection of histamine.

The urobilinogen content of the urine and stools is increased in practically all cases.

Where anemia is slight in degree, the combination of achlorhydria, slight macrocytosis as indicated by calculation of mean corpuscular volume and by the presence of macrocytes in the blood smear, together with a slight degree of bilirubinemia, makes the case highly likely.

Differential Diagnosis: When the macrocytic anemia is part of another disorder such as "aplastic" anemia, "aleukemic" leukemia, or some type of hemolytic anemia, differentiation is important, for vitamin B_{12} or folic acid are of no value. In aleukemic leukemia, sternal marrow examination should reveal a characteristic picture quite different from that of P.A. and in hemolytic anemia. The marrow is normoblastic, not megaloblastic. Even when the macrocytic anemia is accompanied by megaloblastic bone marrow, differentiation is important, since some forms, unlike P.A., are not permanent in character and do not require treatment for the remainder of patient's life. Certain rare megaloblastic macrocytic anemias, furthermore, do not respond to the administration of refined liver extract or to vitamin B_{12}. Some of these are described below.

It is important that diagnosis be established accurately before treatment is initiated. In doubtful cases, a therapeutic test can be very helpful. It is important, however, that the test be made with vitamin B_{12} alone and not with some agent containing iron or other substances in addition, and that the reticulocyte be observed daily for seven to ten days until a positive or negative result has been obtained.

The cobalt contained in the vitamin B_{12} can be labeled radioactively and the absorption of vitamin B_{12} can be thus measured. This provides a means by which defective absorption of vitamin B_{12} from the G.I.T. can be demonstrated even in the absence of anemia, as in treated cases of P.A., and to some extent megaloblastic anemias other than P.A. can be differentiated from the condition. Several different techniques are available, but the most commonly used one, the *Schilling test*, depends on measurement of the excretion of the administered radioactive material in the urine. When radioactive vitamin B_{12} is given by mouth to persons who can absorb it, radioactivity will appear in the urine if the person is "flooded" with an I.M. injection of non-radioactive vitamin B_{12}. Normal individuals have been found to extrete 7 to 22% of the orally administered radioactivity in the urine in twenty-four hours with average of 14%. Patients with P.A. have been observed to excrete only 0 to 2.3% under these conditions. In them the simultaneous administration of intrinsic factor and radioactive vitamin results in increased excretion from 3.1 to 30%.

2) *Sprue and other malabsorption syndromes* can be accompanied by macrocytic anemia or microcytic hypochromic anemia.

3) *Megaloblastic anemia of infancy.* Is common.

4) *Megaloblastic anemia* with Diphyllobothrium latum.

5) *Pellagra.*

6) *Megaloblastic anemia of pregnancy.*

Iron deficiency anemia

By far the most common cause of such anemia is *chronic* blood loss. *Impaired absorption* of iron is rarely an important factor in the development of iron deficiency anemia, however may be seen, for example in Malabsorption syndromes. Vitamin C favors iron assimilation.

Deficiency of iron in the diet alone is rarely a cause of iron deficiency except in infants receiving a milk diet exclusively, and occasionally in elderly people who have depleted their stores by consuming a diet very low in iron.

In children and adolescents the iron needs for *growth* are very important, and it is largely because of the demands made by the ever-expanding blood volume that infants receiving an unsupplemented diet of milk develop iron deficiency. In older children and adolescents, poverty or faulty habits may contribute to the mounting deficiency by causing consumption of a diet too low in iron to supply the needs.

In adult women, the iron requirement during *pregnancy* and *lactation* are factors which may lead to the development of iron-deficiency anemia.

Blood picture in iron deficiency anemia. The anemia is hypochromic and microcytic, with moderate or no reduction in the number of red blood cells and comparatively more marked reduction in hemoglobin. Anisocytosis, poikilocytosis, and polychromatophilia may be marked. Tiny microyctes, "target-like" cells, elliptic cells, and bizarre poikilocytes are also found, as well as a certain proportion of normally filled red blood cells. Reticulocyte count is low. Only in this type of anemia is a substantially reduced MCHC encountered (less than 30%). This hypochromia is more significant than the microcytosis, although the latter may be extreme (MCV 55 to 75). The red blood cell count may be normal or nearly so, or even greater than normal, while the hemoglobin and the hematocrit are greatly reduced. The leukocyte count is normal or slightly reduced.

The bone marrow is hyperplastic and contains an excessive number of normoblasts.

The only form of anemia of this type which is not extremely rare and which may be mistaken for that due to iron deficiency is Thalassemia. Consequently, the discovery of hypochromic microcytic anemia usually calls for a search for causes of iron deficiency and in particular, requires a thorough search for sources of blood loss.

BIBLIOGRAPHY

Brothwell, T. H., Blood 12:409, 1957
Dacie, J. V. and White, Review J. clin. Path. 2:1
Erslev, A. J.: Blood, 10:754, 1955
Beutler, E.: J. Lab. and Clin. Med. 49:84, 1957
Chernoff, A. I.: New England J. Med., 253:322, 365, 1955
Castle: J. Clin. Investing 36:1428, 1957
Pankerd, T. A. J.: Am. J. Med., 22:724, 1957
Girdwood, R. H.: Quart J. Med. 25:87, 1957
Castle, W. B.: Disorders of Blood in Pathologic Physiology, 2nd Ed, 1956
Wintrobe, M. M.: Clinical Hematology, 4th Ed., 1956
Roberts, Difficult Diagnosis, Saunders, 1958
Cart right, Diagnostic laboratory Hematology, 1958
Best, W. Medical Cl. of N. Am. Jan. 1958
Elliott, F.: The Medical Clinics of N. Am., March, 1959
Josephson, A.: The Medical Clinics of N. Am., March, 1959

Contributors Column

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Dr. Howard D. Cohen, M.D., a graduate of Temple University School of Medicine, interned at Temple University Hospital, had one year of residency in general surgery at Atlantic City Hospital and received an MS. in Otolaryngology after completing a three-year residency in the Department of Otorhinology and the Chevalier Jackson Clinic at Temple University Medical Center.

Dr. Warren R. Johnson, Yale Medical School '57, has been serving his internship at the Delaware Hospital, Wilmington and is presently in his second year of Pediatric Residency. Dr. Johnson will be Medical Care Resident in Pediatrics at the Johns Hopkins Hospital, Baltimore as of July 1, 1960.

Dr. James T. Metzger, Duke University School of Medicine '45, was general surgical resident at Duke Hospital, then plastic surgical resident, under Dr. Ferris Smith, Grand Rapids, Michigan and in '53 became Associate in plastic surgery at Duke University. Dr. Metzger is on the active staff of all hospitals in Delaware, and consultant in plastic surgery to Alfred I. duPont Institute and the Veterans Administration Hospital.

Dr. Richard A. Kahlbaugh, chief medical resident at the Delaware Hospital, Wilmington, interned there after his graduation from The George Washington University School of Medicine in 1956.

Elvyn G. Scott, M.T., has been Bacteriologist at the Delaware Hospital since 1936 and is also consultant in bacteriology to the Memorial Hospital, Wilmington. With Dr. W. Robert Bailey of the University of Delaware, Mr. Scott has been co-author of the 6th edition of *Diagnostic Bacteriology*.

In Brief

Unofficial Medical Ambassadors

Medical international relations will get a boost with a $180,000 grant from Smith Kline & French Laboratories which provides scholarships for medical students (eligible after completion of the third year) to work in remote areas of the world. The new program has been announced by the Association of American Medical Colleges. Object: broad clinical experience gained and a knowledge of preventive medicine as practiced abroad. In exchange, the selected Fellow will communicate the most recent medical knowledge of the United States to foreign regions. Medical students must submit applications to the Dean of their medical school.

New Medical Society Officers

Dr. Andrew M. Gehret was named president-elect of the New Castle County Medical Society; Dr. Allen D. King becomes president succeeding Dr. H. T. McGuire; Dr. Frank A. Jones, vice-president; Dr. Harry J. Repman, secretary; Dr. John W. Alden, treasurer and Dr. G. William Martin, Jr., councillor.

Retirement Not an End

Four Wilmingtonians — George S. Long, I. B. Finklestein, Raymond W. Heim and Frederick S. Johnson — retired from careers in business and education — are now devoting their time to a mutual interest of long standing as active members of the board of directors of the Delaware Anti-Tuberculosis Society. All four men are using the vast amount of experience each has accumulated over the years to serve mankind.

Noted

A free vision-spinal-posture screening clinic for school children was held recently in Hockessesn, Delaware. The clinic was sponsored by the Friendship and Liberty Lodges, under the supervision of S. H. Ufberg, chiropractor, and J. D. Paul, optometrist.

New Totals for Blue Shield

An all time high enrollment gain for the first nine months of 1959 is reported by the National Association of Blue Shield Plans. Total membership represents nearly 24% of the United States population; total payments to doctors in behalf of members represents 90% of the total income of all plans for the same period. This points up the extent to which Blue Shield is helping to pay the nation's yearly doctor bills and reflects the continued acceptance by the public of the medical-surgical program offered.

School of Nursing Accredited

St. Francis Hospital School of Nursing has been granted full accreditation by the National League for Nursing, which makes it one of 430 schools of the nation's 1,118 professional schools of nursing to have this status. This process involves application and a seven day inspection of the School by a League team. Dr. Willard Preston is chairman of the school's advisory board.

Take Yo' Pick

According to figures from the Health Insurance Institute, based on a national survey, hospital rates for two-bed semi-private rooms in cities of more than 100,000 population range from a high of $27.80 a day in Oakland, California to a low of $9.29 a day in Montgomery, Alabama. Wilmington, Delaware falls in the middle with $18.62 as an average daily rate — Philadelphia averages $16.48 and New York City, $20.93.

Salk Vaccine Proves Itself

Figures released by Dr. Anthony F. Vitiello, Chairman of the Wilmington Board of Health, show a decline of polio cases in the city from 16 in 1958 to only two in the last year. The state-wide polio record, also showing a considerable drop for 1959, shows that Delaware is one of the few states with a decrease in polio cases. Some credit goes to the inoculation program launched by the Medical Society of Delaware. Persons who have not yet received the fourth booster shots are again urged to do so.

Valuable Service Thrives — (Unfortunately)

The Delaware Poison Information Service, organized by Elmer Fantazier, M.D., Mark Kenyon, Ph.D. and the late Mr. Robert Cathcart, has, in the last fourteen months of service to the public, answered 1,460 telephone calls concerning poisoned individuals and has treated 601 persons at the Poison Center for accidental poisoning. Headquarters are located in the Delaware Hospital; telephone OL 5-3389.

Medical Education the Hard Way

The Association of American Medical Colleges reports that one-third of the medical students in the 1959 graduating class had financial liabilities greater than their total assets. Borrowing was necessary for completion of their medical education.

Services Available

Information on how to obtain the results of research and development in the USSR and other Soviet orbit countries, in the fields of science, technology and medicine are available now by writing the Pergamon Institute, 1404 New York Avenue, N.W., Washington 5, D. C., Executive Director, I. R. Maxwell.

Birth Control Explosion

Birth control as an official policy financed by public funds is becoming a universal question. The experts claim that by the year 2000 the world population will reach 7 billion. Many governments are instituting government-supervised programs to disseminate birth control information; India for one, Japan (where abortion was legalized in in 1958), Pakistan, Ceylon, Malay, Hong Kong and the United Arab Republic. Behind the iron curtain, Poland and Russia are giving attention to population control. In America, the Methodist, United Lutheran,Evangelical Lutheran, Congressional Christian, and Protestant Episcopal churches plus the Central Conference of American Rabbis, have given encouragement to the control of parenthood and the freedom to convey such information as a safe-guard to the well-being of the family and society. Indications now are that the use of public funds to promote birth control could have domestic as well as international repercussions and could even become an issue in the 1960 presidential campaign.

The Deborah Symposium

A forthcoming heart symposium, open to all interested physicians, has been announced by Deborah Hospital, Browns Mills, New Jersey. Congenital heart disease will be the subject of the hospital's second International Symposium to be held April 28-30 in the Bellevue-Stratford Hotel, Philadelphia. There is no registration fee. Deborah Hospital is free, non-sectarian and was established 38 years ago as a tuberculosis institution, expanding its interests in recent years to include the treatment of chest diseases, with emphasis on heart surgery.

Scientists of Tomorrow

Clemson College, S.C., will be host to the second JESSI (Junior Engineers and Scientists Summer Institute) session from June 12-25, 1960. This two-week program is designed to remove the *Guess* from school and college career decisions by giving the student an academic insight into the opportunities open in science and engineering fields. Eligible are boys completing grades 10 and 11 by June who have credits for three to four courses of high school math and/or science. Write: Scientists of Tomorrow, 114 Sylvan Bldg., Portland, Oregon.

The Stress . . . .

According to two physician-biochemists at the National Heart Institute, Bethesda, Maryland, a potent fat-mobilizing pattern or hormone activity has been found in dog experiments which points to stress-induced overactivity of the adrenal glands as producing excessive amounts of cholesterol in the blood. The dog studies are now being extended to volunteers at National Institutes of Health to learn whether the pattern "stress hormones" that raised the blood lipids of dogs has a similar effect on man.

. . . And the Strain.

Experiments conducted at the Army's Walter Reed Hospital show that the strain of responsibility is linked to shorter life. This may explain why physicians, constantly responsible for life, generally have shorter than average life spans.

In monkeys subjected to six hours of strain and then six hours of relaxation, an increase in stomach acidity, believed to be associated with ulcers, occurred during the periods of relaxation rather than stress. Another series of experiments with the same monkeys showed no excess of acidity when the strain was continuous during their waking hours. A possible conclusion is that if a person must worry and tie himself into emotional knots, he should worry all the time rather than alternating between periods of strain and relaxation!

Have You Noticed?

"Men walk from the knee, while women walk from the hip. Men strike matches towards themselves, while women strike away. Men dress to look like other men while women dress to look unique within the current fashion. Men look at their fingernails by cupping their palms and bending their fingers towards themselves while women look at their nails by straightening their fingers palms outward. Men spit flecks of tobacco off their tongues; women pick them off. Men nag their wives for what they do. Women nag their husbands for what they don't do."—according to Dr. Kenneth M. Colby (*A Skeptical Psychoanalyst*, Ronald Press, N. Y.)

Editorials

HERRMAN L. BLUMGART

His many friends in Delaware will join us in sending our congratulations and best wishes to Doctor Blumgart in whose honor a Professorship of Medicine at the Harvard Medical School has been named. Professor at his alma mater, director of the Medical Department at Boston's Beth Israel Hospital, and Editor-in-Chief of *Circulation* are but a few of his accomplishments. His service during World War II not only was a direct stimulus toward providing better patient care to many soldiers but served as and inspiration to the hundreds of medical officers who were fortunate enough to be associated with him. This recent honor is most fitting and deserved.

MEDICAL WRITING:

The current prize contest for an essay on a medical subject by an intern or resident that is being sponsored by the Delaware Valley Chapter of the American Medical Writers Association should be a stimulus for the young physician who says that he cannot write. As has been mentioned repeatedly in these columns, a physician should be able to write. Here is an excellent opportunity for the young trainee to gain valuable experience; perhaps win a cash award. All papers will be reviewed by a group of judges who are chosen for their literary or editorial experience. Merely submitting a manuscript and having it criticized by this panel should be ample compensation for the physician who desires to improve his writing ability.

Doctor John H. Talbott, Editor of the Journal of the American Medical Association, has discussed medical writing in the current (January 23) issue of that journal. He repeats a lesson taught for years by Dean George Meeker of the University of Pennsylvania Graduate School of Medicine —we must struggle through revision after revision, draft after draft, before our composition begins to be presentable. Dean Meeker added a further suggestion—when you think that your paper is completed and in good form, put it away for several months. When you then take it out and read it, you frequently will wonder who in the world wrote such trash.

Despite the general acceptance of the fact that no one can write a good paper in a single draft, it is interesting to note how many papers reach the editorial office fresh from the transcribing tape and the stenographer's typewriter, never having reached the desk of the author.

Doctor Talbott's editorial was stimulated by the publication of a book on "style." We would be foolish indeed not to agree that the book he mentions is excellent and that proper style is indeed desirable. From our limited viewpoint, however, the average physician who is considering writing a paper is more in need of a book aimed at his specific problem. There are many such books but one recently published having all the virtues of the old standbys plus a few of its own is "*The Preparation of Medical Literature*" by Louise Montgomery Cross. If a single book is to be recommended, this is our choice.

LEGAL MANSLAUGHTER:

In a recent (January 21) editorial in the New England Journal of Medicine, the subject of the police chase of stolen cars at dangerous speeds was again discussed. It previously had been editorialized on May 22, 1958 and the editor appeared to be pleased by the action stimulated by his editorial.

In this column for September, 1959 under the title *Five Minutes or Eternity* a plea was made to cut down on the dangerous speed of ambulances and to attempt, by persuasion, to stop their practice of running red lights. We are realistic enough to expect no reply to our small cry; more important, and discouraging, no one seems to care.

Auxiliary Affairs

● The story of a selfless adventure that served a great need—Dr. and Mrs. Daniel Preston in Uganda, Africa.

Doctors' wives often lead very lonely lives as their husbands fulfill the demands of a most time-consuming profession, but, usually they feel compensated by the need and importance of what their husbands do. And once in a while, they get to share in a wondrous adventure.

One of these is Amy Preston, wife of Doctor Dan and a registered nurse as well, who insists that it's against her religion to fly — "*I'm a very devout Coward*," she says. *But!*

In the afternoon on July 31st, Dr. and Mrs. Preston left Idlewild Airport by TWA bound for Entebbe, Uganda, Africa, with stops at Lisbon, Madrid, Algiers, Tunis, Rome, Athens, Cairo, and Khartoum in the Sudan. They finally arrived at their destination at 11:30 p.m. on the ninth of August. That's quite a bit of flying for a self-styled coward.

And why Uganda, Africa? Last January Dr. and Mrs. Preston met the Assistant Bishop of Uganda, Keith Russell, when he visited here in Wilmington and spoke at the Cathedral Church of St. John. When they were all dinner guests of Dean and Mrs. Lloyd E. Gressle of St. John's, Dr. Preston posed a doctor's typical first question, "What is your medical set-up, Bishop Russell — do you have a surgeon?"

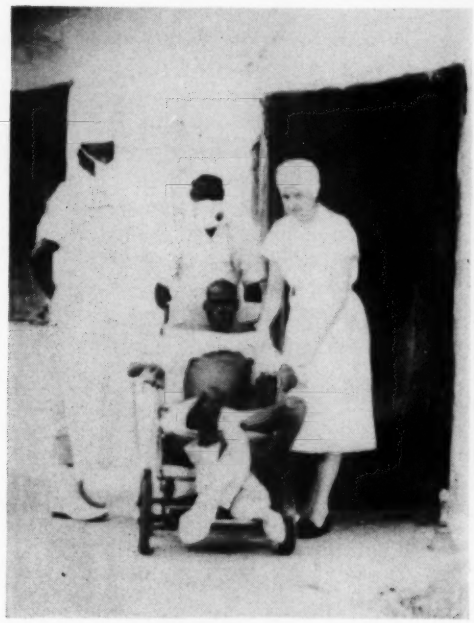
Well, at the little Freda Karr Hospital, and Anglican Mission Hospital in Ngora, Uganda, there are two general practioners and no surgeon, and this is where Dr. and Mrs. Preston went to serve a great need for almost two months.

Their trip was an exciting adventure, sightseeing in cities Mrs. Preston had not visited before — Lisbon, Athens and Cairo — but their experience living and working in Africa among the Ateso tribe which lives in Ngora, an area of Uganda which covers about 250 sq. mi., was the real highlight.

While in Ngora, they lived with Dr. Paul Sparks, a batchelor and one of the two doctors at the hospital. The home Dr. Sparks shared with them was a modest stucco house with tin roof and somewhat primitive facilities. Their needs were served by two natives, Erridati, the cook, and Sam Weirry, a houseboy.

The days were busy for the Prestons. They were awakened each morning at 6:30 A.M. by the sound of the iron gong, calling the hospital workers to their jobs. The staff included the two physicians, Dr. Sparks and Dr. Wright; the director, Mr. Neal Stedman; a dentist, Dr. Knight; Canon Prentice; two English registered nurses; and two native registered nurses who had been trained at the hospital in Kampala, the capital of Uganda.

Amy Preston supervises two native aides—an operating room assistant and a ward dresser—in handling an eighteen year old patient in a wheel chair.



Mrs. Preston standing in front of one of the thatched buildings with the Bishop of Uganda, Stephan Tomasange.

In the course of days at the hospital, where 150 to 160 people would come to the clinic every Monday, Wednesday and almost as many when it was not open, Dr. Preston performed operations of almost every kind: fractures, fibroids, ovarian cysts, removal of tubes, breast abscesses, ceasarians — even a cataract removal with instruments given to him for the hospital by Dr. Norman Cutler.

Mrs. Preston scrubbed with Dr. Dan, as they soon realized that difference in terminology hampered communication with the English-trained nurses. Their greatest handicap, however, was the scarcity of sterile drapes, towels and cloths. The primitive washing by hand, limited materials, and small sterilizing drums, prevented a greater number of operations. Their work was complicated, too, by the fact that almost every native who came into the hospital suffered also with malaria, hookworm, and/or various skin diseases.

All was not work for the Prestons during their African stay. On the 31st of August, they set out on a Safari, stopping overnight with Bishop Russell in Gulu, then 50 miles on to Murchison Falls where they stayed at the beautiful Paraa Safari Lodge on the bank of the Nile in an apartment built last year especially for the Queen Mother of England. They spent one morning cruising on the Nile where they saw hippopotamuses, rhinoceroses, crocodiles, water buffalo, a leopard, baboons and monkeys. They traveled overland in a little Hillman Minx which they procured through their travel agency. Automobile travel was limited to short distances and only in the daytime by the primitive roads and the proximity of wild animals.

Dr. and Mrs. Preston returned to the States at the end of September. The stories of their adventures on their trip are fresh and exciting. Be sure to ask them when you see them.

MAJOR MEDICAL MEETINGS IN DELAWARE

Standing Schedule

Beebe Hospital	General Staff	2nd Friday	Monthly
Delaware Hospital	General Staff	2nd Tuesday	Feb., May, Sept., Dec.
Kent General Hospital	General Staff	3rd Tuesday	Monthly
Memorial Hospital (Wilmington)	General Staff	2nd Tuesday	Jan., March, June, Oct.
Milford Memorial Hospital	General Staff	2nd and last Tuesdays	Monthly
Nanticoke Memorial Hospital	General Staff	1st Thursday	Monthly
St. Francis Hospital	General Staff	4th Tuesday 1st Tuesday	March, May, Oct. December
Wilmington General Hospital	General Staff	4th Tuesday	Jan., April, Sept., Nov.

Kent County Medical Society	Monthly Meeting	3rd Tuesday	September - June
New Castle County Medical Society	Monthly Meeting	3rd Tuesday	September - June
Sussex County Medical Society	Monthly Meeting	2nd Thursday	September - June

Delaware Academy of General Practice	Monthly Meeting	1st Tuesday	September - June
Delaware Pathology Society	Weekly Meeting	Each Friday	

Special Schedule

Medical Society of Delaware and The Royal Society of Medicine	Trans-Atlantic Clinico -Pathological Conference	Delaware Academy of Medicine	April 20, 1960
Medical Society of Delaware	Annual Meeting	Rehoboth, Delaware	September 8, 9, 10, 1960

LECTURE COURSE

Subject: Basic Electrocardiography

Schedule: Part I

Time — Every Thursday afternoon 4-5 p.m.
Dates: From October 29, 1959 through February 25, 1960

Place: Memorial Hospital, Wilmington

Schedule: Part II

Time — Same as for Part I
Dates: March 3rd through March 31st, 1960
Arrangements must be made for Part II only.

For full details regarding this series write to the Director of Medical Education, Memorial Hospital, Wilmington

TWO-WAY RADIO CONFERENCES FOR THE COMING MONTH

Sponsorship: *Medical Society of Delaware, Pennsylvania Hospital, Smith Kline & French Laboratories.*

Date *Topic and Faculty*

Feb. 23—"Cardiac Lesions Amenable to Surgery." Julian Johnson, M.D., Prof. Surgery, University of Pennsylvania School of Medicine.

Mar. 1—"Common Orthopedic Problems of Children," Jesse T. Nicholson, M.D., Orthopedic Surgeon to Pennsylvania Hospital.

Mar. 8—"Comparison of BMR, PBI, I^{131} and Cholesterol," George R. Fisher, III, M.D.

Mar. 15—"Mechanism, Etiology and Management of Dysmenorrhea," Craig W. Muckle, M.D., Assoc. Obstetrician and Gynecologist, Penna. Hospital.

Mar. 22—"Laboratory Workup of the Patient with Anemia," Edward H. McGehee, M.D.

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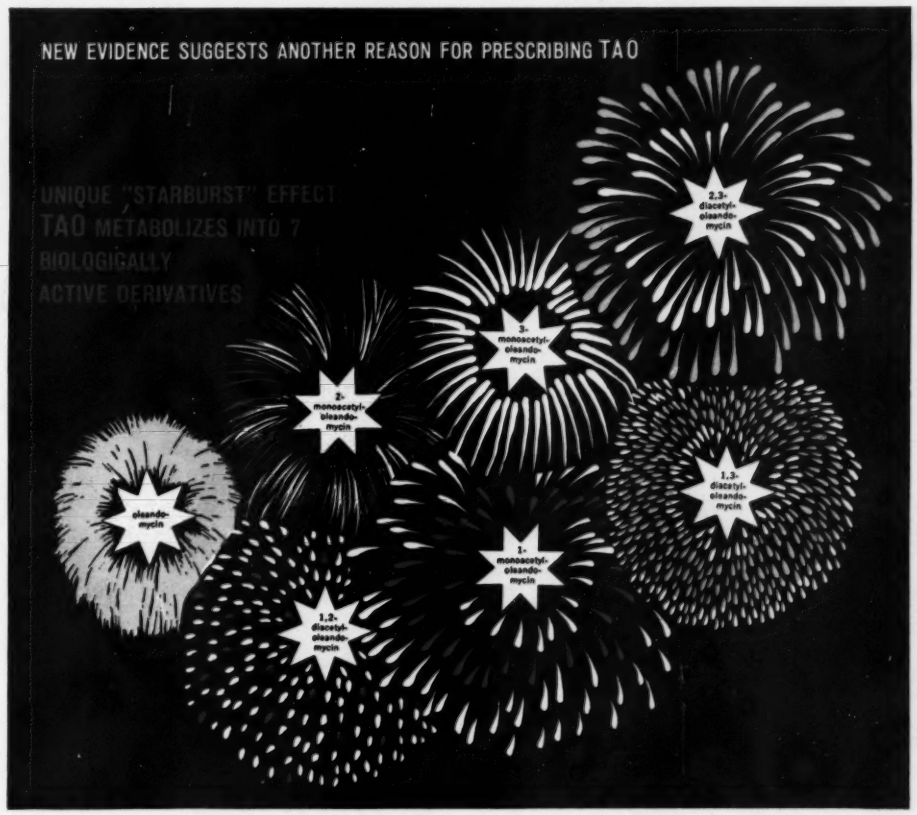
Clinical reports on Dartal: 1. Edisen, C. B., and Samuels, A. S.: A.M.A. Arch. Neurol. & Psychiat. *80*:481 (Oct.) 1958. 2. Ferrand, P. T.: Minnesota Med. *41*:853 (Dec.) 1958. 3. Mathews, F. P.: Am. J. Psychiat. *114*:1034 (May) 1958.

SEARLE



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In light of these findings, take another look at TAO performance: • 92% success in published cases of Gram-positive respiratory, skin, soft tissue and genitourinary infection • Effective against 78% of 64 "antibiotic-resistant" epidemic staphylococci. (In the same study, chloramphenicol was active against 52%; erythromycin against only 25%)[3] • No side effects in 94%; infrequent reactions mild and easily reversed • Quickly absorbed • Highly palatable.

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1. English, A. R., and McBride, T. J.: Proc. Soc. Exper. Biol. & Med. 100:880 (Apr.) 1959. 2. Celmer, W. D.: Antibiotics Annual 1958-1959, New York, Medical Encyclopedia, Inc., 1959, p. 277. 3. English, A. R., and Fink, F. C.: Antibiotics & Chemother. 8:420 (Aug.) 1958.

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Caffeine ..... gr. ½
Codeine Phosphate .... gr. ¼

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Caffeine ..... gr. ½
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that which
requires morphine

AND IN
fevers
dry,
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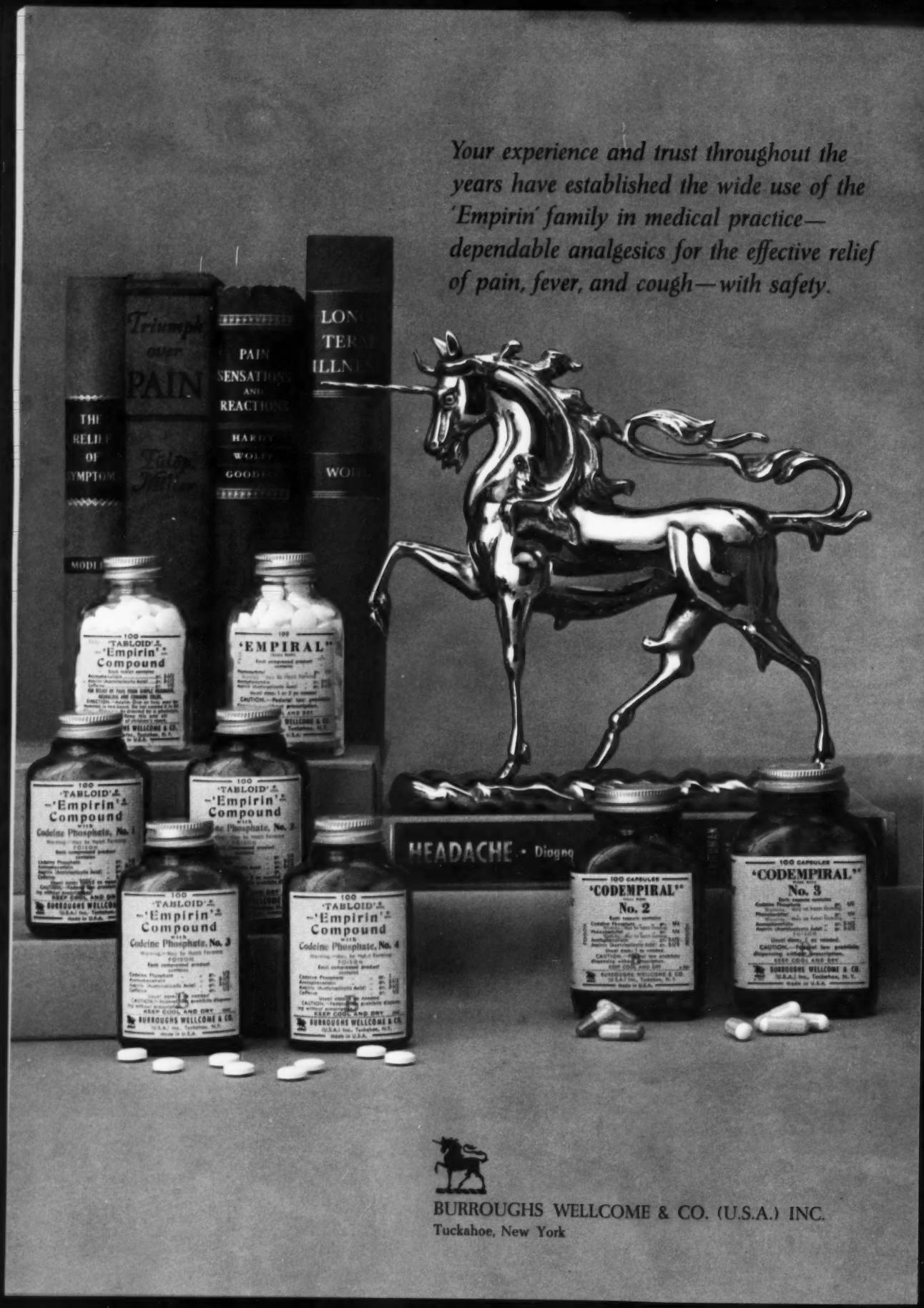
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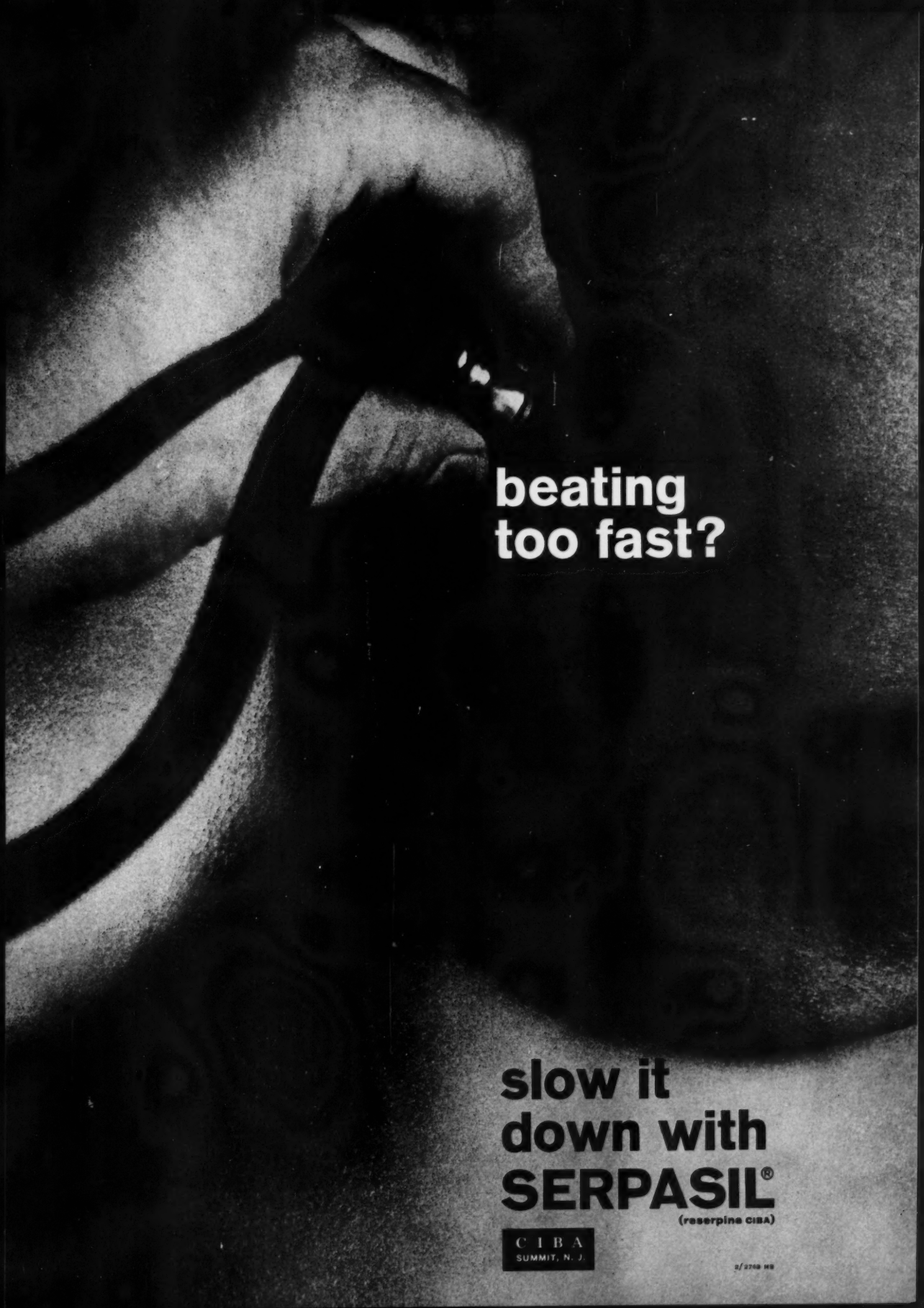
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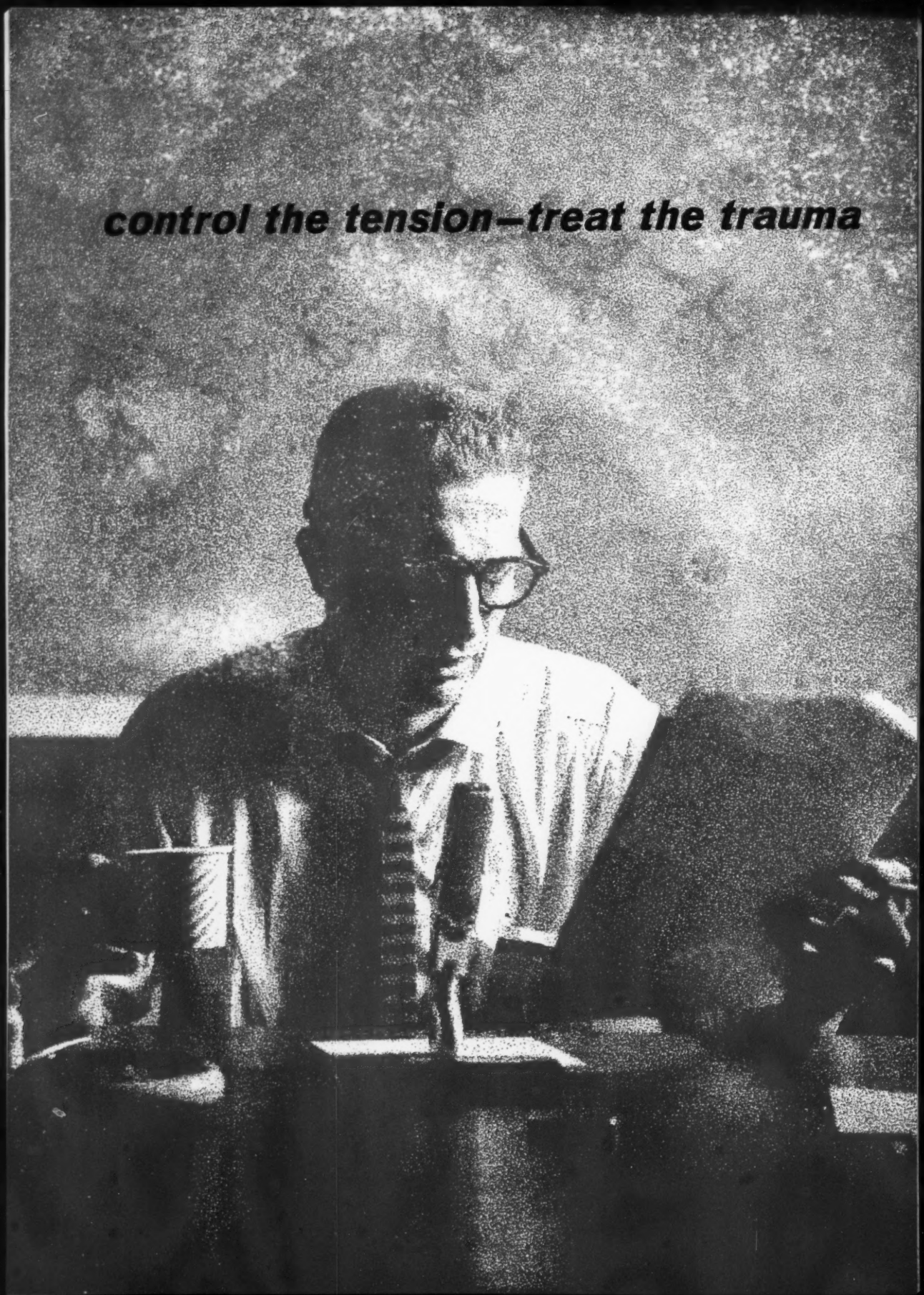
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"superior to aspirin" — ". . . evidence seems to indicate that the concurrent administration of para-aminobenzoic and salicylic acid [as in Pabalate] produces a more uniformly sustained level for prolonged analgesia and, therefore, is superior to aspirin in the treatment of chronic rheumatic disorders."[1]

In each yellow enteric-coated PABALATE tablet:

Sodium salicylate (5 gr.)	0.3 Gm.
Sodium para-aminobenzoate (5 gr.)	0.3 Gm.
Ascorbic acid	50.0 mg.

For the patient who should avoid sodium

PABALATE-SODIUM FREE

Same formula as Pabalate, with sodium salts replaced by potassium salts (pink)

For the patient who requires steroids

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Pabalate with Hydrocortisone

In each light blue enteric-coated PABALATE-HC tablet:

Hydrocortisone	2.5 mg.
Potassium salicylate (5 gr.)	0.3 Gm.
Potassium para-aminobenzoate (5 gr.)	0.3 Gm.
Ascorbic acid	50.0 mg.

1. Ford, R. A., and Blanchard, K.: Journal-Lancet 78:185, 1958.

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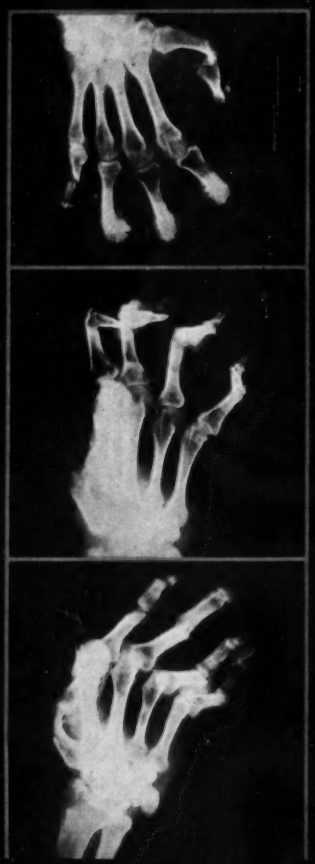

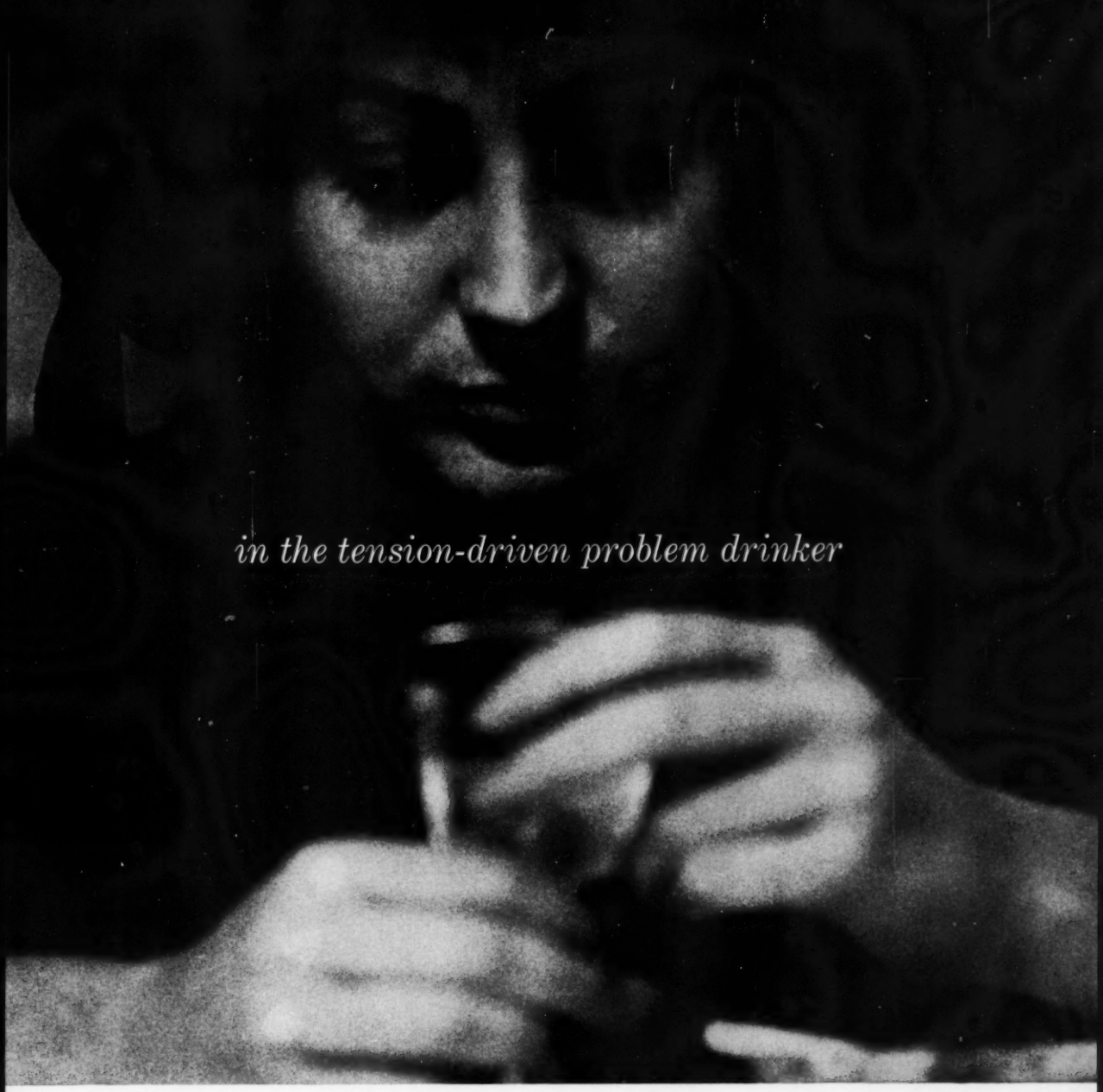

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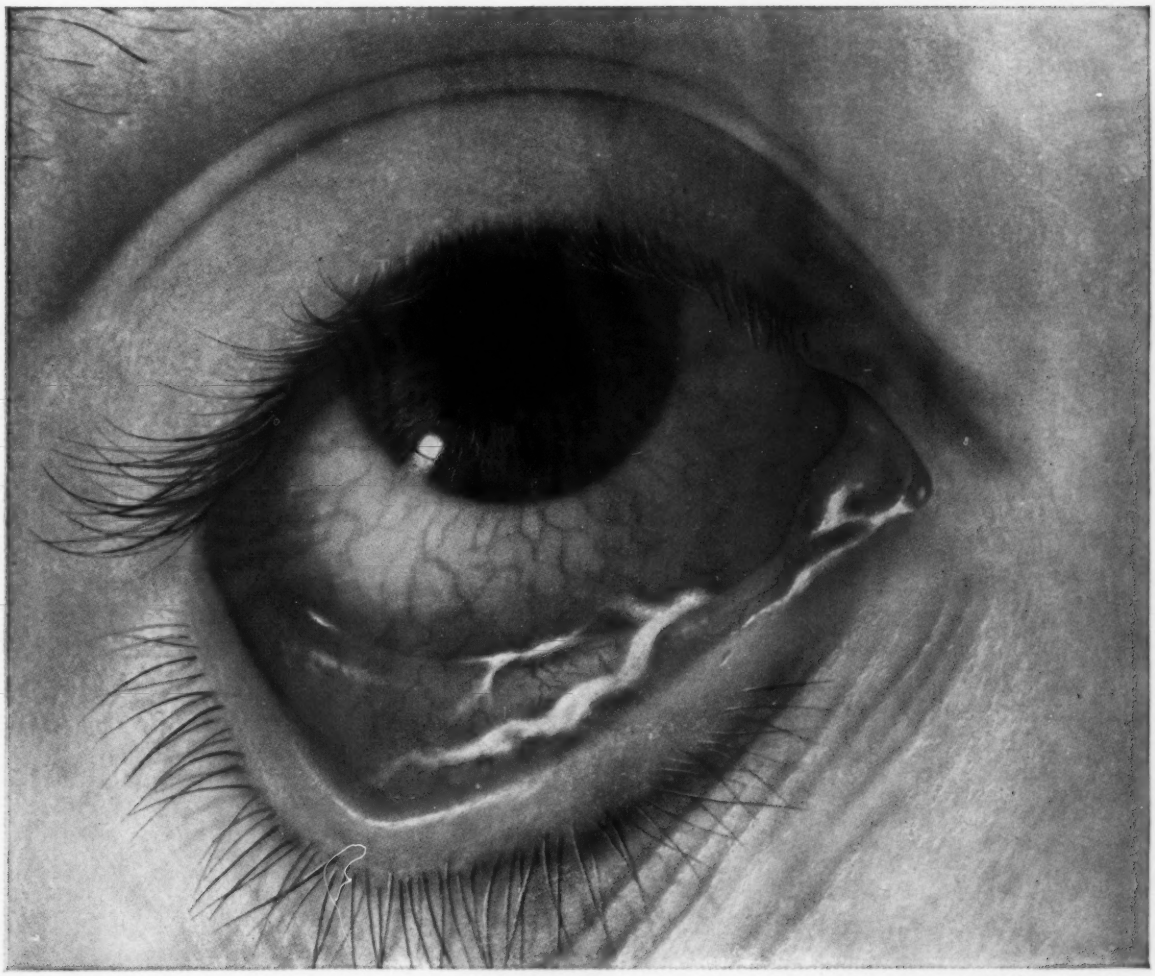

no irritating crystals[1] · uniform concentration in each drop[2]

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PREDNISOLONE 21-PHOSPHATE-NEOMYCIN SULFATE

2,000 TIMES MORE SOLUBLE THAN PREDNISOLONE OR HYDROCORTISONE

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1. Lippmann, O.: Arch. Ophth. **57**:339, March 1957.
2. Gordon, D.M.: Am. J. Ophth. **46**:740, November 1958.

supplied: 0.5% Sterile Ophthalmic Solution NEO-HYDELTRASOL (with neomycin sulfate) and 0.5% Sterile Ophthalmic Solution HYDELTRASOL®. In 5 cc. and 2.5 cc. dropper vials. Also available as 0.25% Ophthalmic Ointment NEO-HYDELTRASOL (with neomycin sulfate) and 0.25% Ophthalmic Ointment HYDELTRASOL. In 3.5 Gm. tubes.

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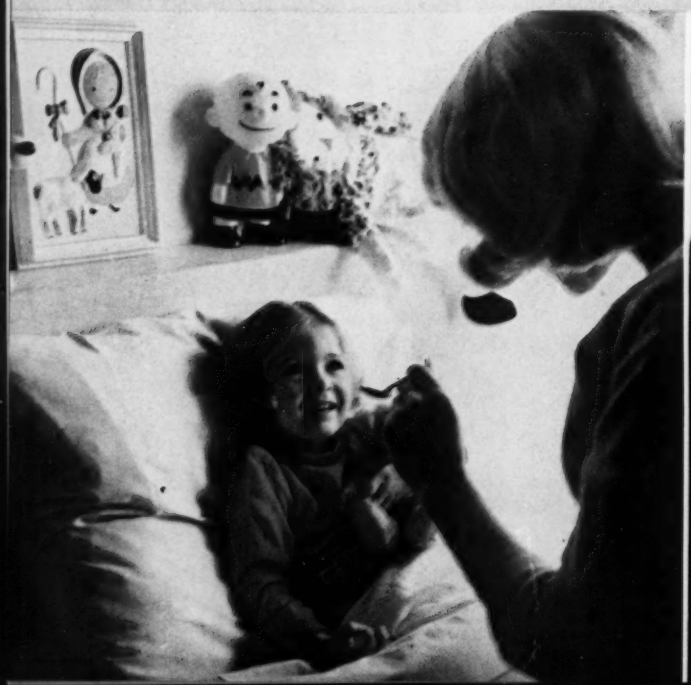
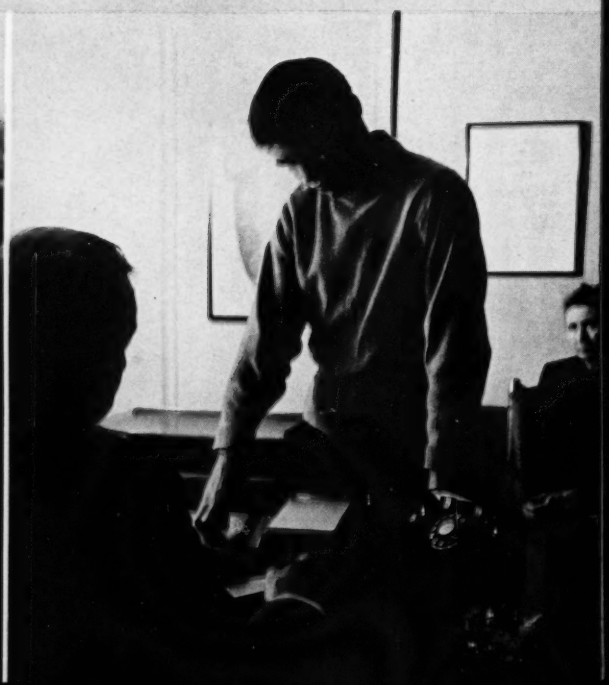
ORAL ROUTE PROVIDES HIGHER BLOOD LEVELS THAN INTRAMUSCULAR PENICILLIN G

IMPROVED ANTIBIOTIC ACTION FROM ISOMERIC COMPLEMENTARITY





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POTASSIUM PENICILLIN-152

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REDUCED RATE OF INACTIVATION BY STAPH PENICILLINASE

MANY STAPH STRAINS MORE SENSITIVE TO SYNCILLIN IN VITRO

BRISTOL

FOR HIGHLY EFFECTIVE THERAPY OF THE LARGE VARIETY OF INFECTIONS CAUSED BY SUSCEPTIBLE PATHOGENS... NEW

SYNC

Significance of complementary action of isomers in SYNCILLIN

The antibiotic effect of the clinically available mixture, SYNCILLIN, is greater than that of either of its two component isomers alone against many important pathogens, including some penicillin-resistant staphylococci. This phenomenon has been described as *Isomeric Complementarity.*

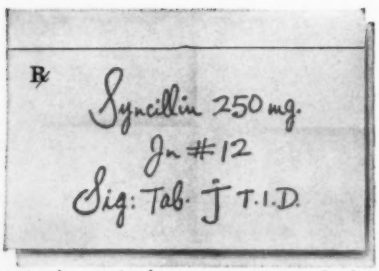
Significance of higher blood levels with SYNCILLIN

Higher blood levels may be of value with organisms of only moderate penicillin sensitivity where doubling the blood concentration may be essential for effective bactericidal action. In addition, these higher levels may be necessary where there is infection in areas with a poor blood supply.[6] Under these circumstances a higher blood concentration may provide the increased diffusion pressure required to deliver adequate amounts to the tissue. Also, antibiotic activity of SYNCILLIN is directly proportional to oral dosage. Increasing the dosage may, therefore, enhance the drug's effectiveness in certain cases.

Efficacy of SYNCILLIN against staphylococci and other resistant organisms

Studies have shown that SYNCILLIN is effective *in vitro* against 60 to 75% of hospital "staph" strains, while penicillin G and penicillin V are now effective against only 30 to 50%.[1, 2] Therefore, if clinical judgment indicates the use of penicillin, SYNCILLIN would be expected to be the most effective. However, since some strains are still resistant to SYNCILLIN as well as to the other penicillins, cultures and sensitivity tests should be performed where indicated by clinical judgment.

There have recently been reports of decreased efficacy of penicillin in streptococcal[3] and gonococcal[4, 5] infections. The emergence of penicillin-resistant gonococci appears to be associated with an increase in the incidence of gonorrhea all over the world. When a less sensitive strain is encountered the higher blood levels produced by SYNCILLIN may be most helpful.



major therapeutic advantages accompany molecular asymmetry

I L L I N™

Relation of intermittent high blood levels of SYNCILLIN to antibacterial efficacy

SYNCILLIN, like all clinically available penicillins, is bactericidal. Periodic high blood concentrations are sufficient to permit complete eradication of sensitive pathogens. Continuous high blood levels are not required with **SYNCILLIN**. According to Eagle,[7] "Soon after penicillin attains effective concentrations, the bacteria cease multiplying; and the bacteriostatic effect persists for a number of hours after penicillin has fallen to concentrations that are wholly ineffective....The therapeutic significance of this postpenicillin recovery period is enhanced by the fact that the recovering bacteria, damaged but not killed by the previous exposure to penicillin, are abnormally susceptible to the host defenses. In consequence, the bactericidal process *in vivo* continues for many hours after the drug itself has fallen to ineffective concentrations."

Reduced rate of inactivation of SYNCILLIN by staph penicillinase

Bacterial resistance to penicillin has been attributed to the action of penicillin-inactivating enzymes produced by the invading organisms. **SYNCILLIN** is less affected by staphylococcal penicillinase than either of its component isomers. Further, **SYNCILLIN** is shown to be less inactivated by this enzyme than penicillin V and penicillin G. Penicillinase from *B. cereus* likewise inactivates **SYNCILLIN** less rapidly than penicillin V and G. But this would not impede the therapeutic use of this penicillinase in allergic reactions. This is because the massive dosage with which this enzyme is administered would effectively destroy **SYNCILLIN** in the body.

References: 1. Wright, W. W.: Microbiology Report to Bristol Laboratories Inc. 2. Kligman, A.; Morigi, E. M. E.; Wheatley, W. B., and Albright, H.: Paper presented at the Seventh Antibiotic Symposium, November 4-6, Washington, D.C. 3. Editorial: New England J. Med. **261**:305 (Aug. 6) 1959. 4. King, A.: Lancet **1**:651 (March 29) 1958. 5. Epstein, E.: J.A.M.A. **169**:1055 (March 7) 1959. 6. Kass, E. H.: Am. J. Med. **18**:764 (May) 1955. 7. Eagle, H.: J. Bact. **58**:475, 1949.

Indications: **SYNCILLIN** is recommended in the treatment of infections caused by pneumococci, streptococci, gonococci, corynebacteria, and penicillin-sensitive staphylococci. In addition, **SYNCILLIN** is effective against certain strains of staphylococci resistant to other penicillins. **SYNCILLIN**, like other oral penicillins, is not recommended at the present time in deep-seated or chronic infections, subacute bacterial endocarditis, meningitis, or syphilis.

Dosage: 125 mg. or 250 mg. three times daily, depending on the severity of infection. Larger doses (e.g., 500 mg. t.i.d.) may be used for more severe infections. **SYNCILLIN** may be administered without regard to meals. Beta hemolytic streptococcal infections should be treated with **SYNCILLIN** for at least ten days.

Precautions: At the present time it is not possible to draw definite conclusions regarding the incidence of allergenicity to **SYNCILLIN** or its cross-allergenicity with natural penicillins. *Therefore, the usual precautions for oral penicillin therapy should always be observed.* Patients with histories of asthma, hay fever, urticaria, or previous reactions to penicillin should be watched with special care. Administration of oral penicillin, in rare instances, may provoke acute anaphylaxis, particularly in penicillin-sensitive individuals.
Diarrhea has been reported occasionally following heavy dosage. If this occurs, lengthen the interval between dosages.
If superinfection occurs during therapy, appropriate measures should be taken. Since some strains of staphylococci are resistant to **SYNCILLIN** as well as to other penicillins, cultures and sensitivity tests should be performed where indicated by clinical judgment. As is true with all antibiotics, clinical response does not always correlate with laboratory bacterial sensitivity reports.

Supply: 125 and 250 mg. tablets, bottles of 25 and 100. 125 mg. powder for oral solution, 60 ml. vials.

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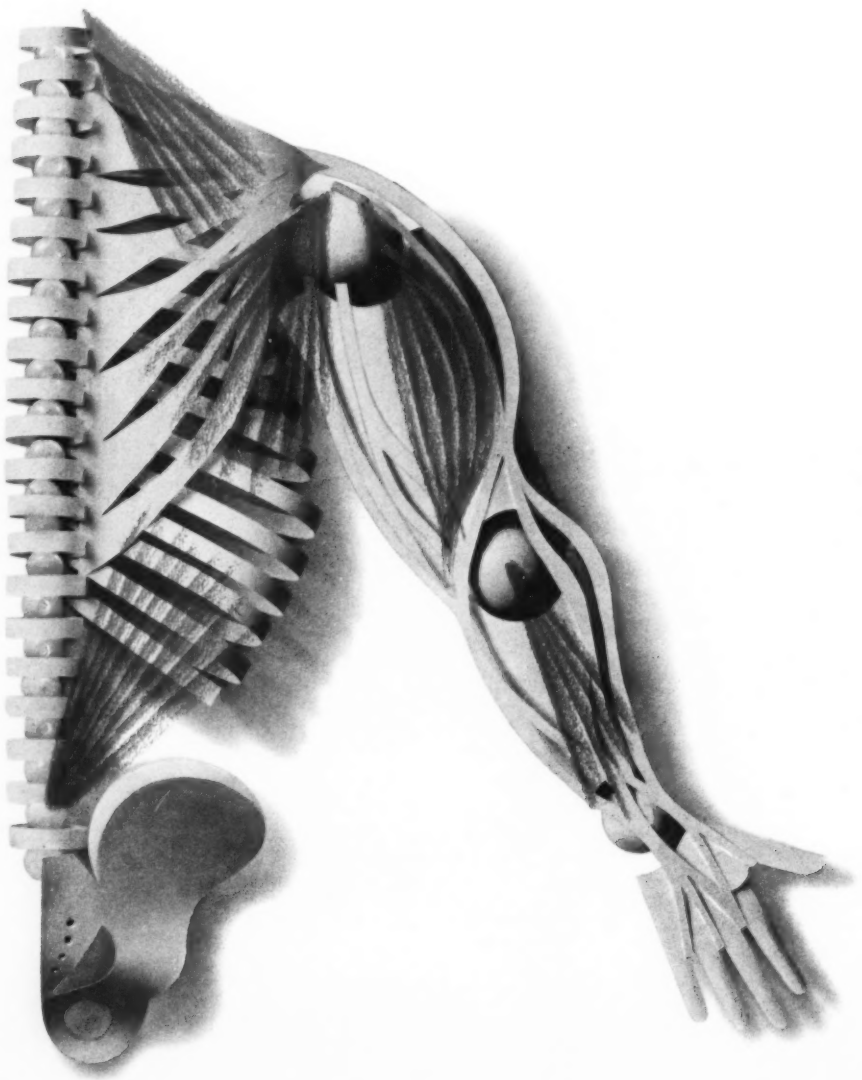

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Kuge, T.: Submitted for publication.

"In 86 percent of the patients there were excellent or good results. . . . Relief of pain was noted by the patients' statements, by the diminished need for analgesic drugs, and by improved sleep." (154 patients.)
Wein, A. B.: The Use of Carisoprodol in Orthopedic Surgery and Rehabilitation. Proceedings of the Symposium on The Pharmacology and Clinical Usefulness of Carisoprodol. Wayne State University Press, Detroit, 1959, p. 156.

In a double-blind study, SOMA was reported to be "clinically effective to a highly significant degree." (92 patients.)
Cooper, C. D., and Epstein, J. H.: The Clinical Evaluation of Carisoprodol by a double-blind technique. Ibid. p. 97.

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Rapid action—starts to act quickly

Sustained effect—relief lasts up to 6 hours

Easy to use—usual adult dose is one 350 mg. tablet 3 times daily and at bedtime

Supplied—as white, coated, 350 mg. tablets, bottles of 50.
Also available for pediatric use: 250 mg. orange capsules, bottles of 50.

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BIBLIOGRAPHY: 1. Berger, F.M., Kletzkin, M., Ludwig, B.J., Margolin, S. and Powell, L. S.: J. Pharm. Exp. Ther. 127:66 (Sept.) 1959. 2. Leake, Chauncey D.: Proceedings of the Symposium on The Pharmacology and Clinical Usefulness of Carisoprodol, Wayne State University Press, Detroit, 1959, p. 8. 3. Kestler, Otto: Ibid. p. 143. 4. Proctor, Richard C.: Ibid. p. 122. 5. Berger, Frank M., Ibid. p. 25. 6. Goodgold, Joseph, Hohmann, Thomas and Tajima, Toshihiro: Ibid. p. 66. 7. Gammon, George D. and Tucker, Samuel: Ibid. p. 70. 8. Baird, Henry W. and Menta, Dominic A.: Ibid. p. 85. 9. Cooper, C. David and Epstein, Jerome H.: Ibid. p. 97. 10. Korst, Donald R., Gerard, R. W., Miller, James G., Small, Iver F., Graham, I. J. and Winkelman, Eugene I: Ibid. p. 104. 11. Friedman, Arnold P.: Ibid. p. 115. 12. Trimpi, Howard D.: Ibid. p. 150. 13. Wein, Arthur B.: Ibid. p. 156. 14. Olds, James and Travis, R. P.: Ibid. p. 39. 15. Hess, Eckhard H., Polt, James M. and Goodwin, Elizabeth: Ibid. p. 51. 16. Phelps, Winthrop M.: Ibid. p. 131. 17. Spears, Catherine E.: Ibid. p. 138. 18. Hyde, L. P. and Hough, Charles E.: Ibid. p. 166. 19. Spears, Catherine E. and Phelps, Winthrop M.: Arch Pediat., 76:287 (July) 1959. 20. Phelps, Winthrop M.: Arch. Pediat., 76:243 (June) 1959. 21. Friedman, Arnold P.: Paper presented at Scientific Meeting, New York State Society of Industrial Medicine, Inc., New York, Sept. 30, 1959. 22. Frankel, Kalman: Ibid. 23. Fransway, Robert L.: Ibid. 24. Kuge, T.: Unpublished reports.

Literature and samples on request WALLACE LABORATORIES, New Brunswick, New Jersey

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